THE ACUTE BACTERIAL DISEASES

Their Diagnosis and Treatment

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PHILADELPHIA AND LONDON

1948

TO

My colleagues at Gallinger Municipal Hospital

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PHILADELPHIA

PREFACE

The old order changeth, yielding place to new. Especially has this been true of the swift succession of events which have contributed within the past few years to our knowledge of the acute bacterial diseases. Change has been most apparent in the field of therapy, where sulfonamides, penicillin and streptomycin were all introduced within the space of a few short years. Less dramatic and therefore more easily overlooked have been the changes and improvements in the laboratory procedures used for diagnosis. A third change has taken place in the attitude of the physician toward the bacterial diseases. In the past his interest was confined mostly to their clinical features and pathology. This was reflected in the nomenclature used, which was either clinical (such as "scarlet fever") or pathological (such as "lobar pneumonia"). Even though the bacteria responsible for most of the acute bacterial diseases had been identified for many years, the disease was seldom named after the micro-organism that caused it. Now that several therapeutic agents have been discovered, each of which is effective against certain micro-organisms and useless against others, it has become imperative to identify each disease according to its etiologic agent. Physicians are now in the process of adjusting themselves to think of the infectious diseases in this manner.

This book is written with the purpose of combining the new order of diagnosis and treatment with that which is worthwhile in the old order. It is intended as a practical guide for physicians and interested students.

In the first chapter certain general factors in the diagnosis of the infectious diseases are considered, and the acute infectious diseases are then grouped together according to their outstanding clinical features. Our purpose in so doing is to aid the physician in narrowing the presumptive diagnosis to one group of diseases. Further diagnostic procedures may then be carried out by consulting the individual diseases. In the next four chapters we have discussed the general measures available and the principal agents employed in the treatment of the bacterial diseases: serums, sulfonamides, penicillin and streptomycin. We have attempted to answer the following questions concerning each of these: In what diseases and under what conditions does it work? How much should be given and by what method? What untoward effects may result from its use?

The remainder of the book has been devoted to a discussion of individual diseases. These have been classified according to the etiologic agent responsible for them. Diseases which are similar in their clinical characteristics have been grouped together whenever possible. Part II

PREFACE

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comprises the diseases caused by the cocci and Part III those caused by bacilli In the latter group there is a subclassification according to the most frequent portal of entry the gastro intestinal tract the respiratory tract or the skin In Part IV are the diseases primarily due to exotoxins In the final chapter a number of less frequent or less important bacterial infections are taken up briefly

In the discussion of the individual diseases the following questions have been considered How can the diagnosis be made with rapidity and yet with certainty? How should the disease be treated? What can be expected as a result of the treatment?

Complete details of epidemiology and pathology have not been included in every instance Instead because of the practical objectives of the book we have attempted to utilize in discussing a disease only those details of epidemiology pathogenesis and pathology which have a direct bearing on diagnosis prognosis and treatment For the same reason we have occasionally incorporated information regarding the technics of a laboratory test where we felt that such details would help the clinician to appraise the value of the test or would aid him in getting optimal results from the examination Here as elsewhere the distance between clinic and laboratory must be shortened

Only the acute forms of tuberculosis have been considered because these are the ones likely to be confused with acute infections caused by other bacteria and because chronic tuberculosis is usually treated in special institutions by a specialized group of physicians and often requires the use of certain procedures such as pneumothorax and thoracic surgery which are outside the scope of this volume

Wherever possible this book is based upon cases personally observed at the Gallinger Municipal Hospital and in private practice These now number over seven thousand patients Numerous persons have contributed to the collection of the data used Among these I would like to thank particularly the George Washington University Fellows in Medicine who have studied these patients with me They are Drs Clarence R Hartman Harry A Feldman Mark H Lepper Edith Dumoff Stanley Harold L Hirsh Jean J Vivino William W Zeller and Jay A Robinson

I am indebted to a number of persons who read and constructively criticized one or more chapters Drs Thomas McP Brown J Keith Cromer Clayton B Ethridge James J Feffer Maxwell Finland Sol Katz Manson Meads David Rutstein and Thomas C Thompson

I wish to express particular gratitude to Drs John H Hanks Carl C Dauer and Mark H Lepper each of whom read all or a large part of the manuscript and offered many valuable suggestions My secretaries Mrs Florence S Stolar and Miss Madeline Brown have been of invaluable assistance

Washington D C HARRY F DOWLING
January 1948

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Part I

DIAGNOSIS AND TREATMENT OF THE ACUTE BACTERIAL DISEASES

1 *Diagnosis of the Acute Bacterial Diseases*

When bacteria cause infections in the human body they produce a wide variety of symptoms and signs and many diverse syndromes Nowhere in the sphere of medicine is the physician called upon to exert more diagnostic acumen than in the field of the infectious diseases Since skill in diagnosis is the product of years of training at the bedside it cannot be transferred to the printed page Nevertheless we shall attempt in this chapter to give some aid to the process of diagnosis by classifying the disease syndromes into groups based upon the major clinical features and by emphasizing the important clinical and laboratory characteristics of the diseases within each group

Infectious diseases fall roughly into two groups first those in which *the disease is obviously localized to one organ or locality* and second those with symptoms and signs of generalized infection only Pneumococcic pneumonia is an example of a disease in the first group and typhoid fever an illustration of one in the second group In an occasional case in spite of the fact that the infection is situated in only one organ or location *there may be no clinical features to point* to a localized infection and the disease may be erroneously diagnosed as a generalized infection In most instances however a careful history and physical examination will enable the clinician to determine whether the infection is localized to a single organ and will at least provide clews as to the organ organ system or area involved Laboratory or other special examinations should then be performed to verify the presence of infection in the suspected site and to determine the etiologic agent For instance *if the patient has* had a chill followed by cough and expectoration of blood tinged sputum an infection in the lung would be suspected—most likely pneumonia If the characteristic signs of lobar consolidation are present the diagnosis will be established with a reasonable degree of certainty but if physical examination of the lungs reveals no abnormal signs *or only a few non* descript rales further examinations will be needed A roentgenogram of the chest or typing of the sputum for pneumococci or both will then be resorted to as the next step

one or several of these cultures will show growth by the following morning We have not found any advantage in taking blood for culture at the time the temperature is at its height

Blood for culture is usually taken from a vein Arteries also have been recommended but we have not found a higher incidence of positive cultures from this source than from veins The sternal marrow however will sometimes yield a positive culture when blood from a vein will not

Body fluids directly in contact with an infected organ or area are often more likely to contain bacteria than the blood Consequently whenever cerebrospinal pleural pericardial peritoneal or synovial fluids have been removed they should always be cultured (and otherwise appropriately examined to detect the presence of micro-organisms) if a bacterial infection is suspected Cultures of urine or feces *should* be made in any case where bacterial infection of the urinary or intestinal tract is likely

Some organisms are more readily obtained upon animal inoculation than *upon* culture In such cases a sufficient amount of fluid should be obtained and inoculation performed as soon as is practicable

Agglutination tests are valuable in the diagnosis of the generalized infections Even though antibodies do not usually appear in the blood for a week or two after the onset of an infectious disease it is nevertheless advisable to perform an agglutination test at the time of the initial examination so that a base line may be obtained against which succeeding tests (usually done at weekly intervals) may be measured

Diseases and Syndromes Characterized Mainly by Fever

The infectious diseases which are characterized especially by signs and symptoms of a generalized infection will be considered first Since fever is usually the most prominent and sometimes the only discernible clinical feature a few preliminary remarks upon fever itself are necessary Elevation of the temperature occurs invariably in bacterial infections except under the following circumstances (1) the infection is so minor that the patient s body is not stimulated to produce fever (2) debility is so extreme or the infection is so overwhelming that the patient is unable to respond with fever

TYPES OF FEVER

Regular continuous or sustained fever is said to occur when the temperature remains at all times above normal limits and the diurnal temperature variation is not more than two degrees Fahrenheit

Intermittent fever is present when there are regularly recurring bouts of fever separated by periods of normal temperature

Remittent fever is fever in which the diurnal variation is two degrees Fahrenheit or more but in which a certain amount of fever remains during the intervals between the peaks

If the clinical features do not point to one location attempts should be made to find out whether one of the generalized infections is present *In some cases the identity of the generalized infection can be established* by the presence of certain significant features in the history and physical examination in other cases laboratory and other special examinations must be employed before a conclusion can be reached

Since fever is the one outstanding clinical feature present in those infectious diseases which do not exhibit any significant abnormality in one organ or locality we have placed all such conditions under the heading of fevers and grouped them together in Table 1

A characteristic feature of many infectious diseases is a skin eruption On the basis of the appearance of the rash its location and the order of occurrence and frequency of the lesions a definite diagnosis can be made in some cases while in others these features will help to narrow down the possibilities For this reason we have attempted to bring together in Table 2 all the *important infectious diseases characterized by a rash* along with certain other noninfectious diseases which may be easily confused with them

Other areas or organs frequently affected during the course of infectious diseases are the pharynx the meninges the joints and the lungs The differential diagnosis of the first three of these will be discussed in the present chapter while the differential diagnosis of pulmonary infiltrations is covered in the chapter on pneumonia (pages 110 to 115)

The purpose of the tables is merely to suggest the possibility of a particular disease and to point out the more important diagnostic features of it For further information about the diagnosis of any bacterial disease the reader should refer to the section on that specific disease

Suggestions Concerning Laboratory Tests

Blood cultures are frequently utilized to diagnose fevers which present no localizing signs In certain other bacterial diseases also they are helpful and sometimes necessary for the purpose of determining the exact etiologic agent Furthermore they aid the clinician in arriving at *a prognosis and in determining the results of treatment* Since blood cultures are important they should be taken carefully and in accordance with certain general principles A medium should be used which is suitable for growing the organisms the presence of which is suspected the proper volume of blood should be added to a given amount of medium and the mixture should be placed in the incubator as soon as possible thereafter If the diagnosis depends especially upon the outcome of the blood culture and specific treatment which might be life saving is being withheld until the result of the culture is known the common practice of taking daily blood cultures will often result in too much loss of time We have found that a satisfactory method is to take several specimens of blood at hourly or even more frequent intervals In many instances

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Group III. Diseases H vi g Cl ical Features Pointing to One Organ or Part Which Are Frequently Observed ith Onset by the Evidences of Generalized Infection

Pn m ia, bacterial	Rg or I	N	N	None	Normal or al levated	Cold aggl tinins, x-ray f l gs	109
Pi m a, bact rial	Rg	N ne	None	N	Elev ted	pu m examination, blood cult re ray of lungs	
Rocky M tai potted f er	Rg or Ir	All	N ne	Occas onal	N, les ed or normal	A glu na m est, complement f xat on test	
Typh f er	Rg or I	All	N ne	Occas onal	l lev ed or normal	Agglut nat test, complement fi tion test	
W il disease	Rg or I	Occas l	N	None	Ele ted	Aggl tination test, in ection of blood t guinea pigs	

Group IV. N fectious Diseases Wh h A e Accompanied by Fever and Are Freque tly Confused th Generalized Infect us Diseases

C rc nom nous parts of th body	I	None	None	N	Normal or l lev t d	Biop y of neoplasm	
Hyperse ti ty to drugs and an biot cs	I	Frequent	Occasional	Rare	Normal or al lev ted	History nd lin cal features	51 54 & 99
Lymph m							
Hodgk s disease	I	Non	Freque t	Freq ent	Freq tly lev ted	B psy of lymph nodes	
Leukemia	I	None	Freque t	Freq ue t	l ally lev ted	E fre ial leukocyt cou t ternal b s y	
Lymphosarcom d thers	I	N	Freq t	Freq t	F eq en ly le t d	B p y of lymph des	
Sarcom in nous parts of th body	I	N ne	Non	N	Norm l l lev t d	B p y f eoplasm	
Serum kness	I Rg or be t	Freq t	Freq t	Rar	Norm l al l ed	H tory nd l ic l f t res	49
Dissem nated l p rythema tosus	I	Freq t	†	Oc sa nal	Lo	B y of k	
Periarteritis od sa	I or Rg	F eque tly [illegible] t cous od les occ nally th m	N	N	Usually [illegible] ted	B p y f m sel	

Rg = egul h gh f I = regul f R = mitt t fev I = term tt t f
† Th reg nal lymph odes th re f h rash us lly larged
‡ D scussed d th ari us ba t which use these ect ns

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TABLE 1

Generalized Infectious Fevers and Diseases Which May Be Confused with Them

Group I Diseases in Which Clinical Features Pointing to One Organ or Part Are Seldom, If Ever, Present

Name	Type of Fever*	Rash	General Lymphadenopathy	Splenomegaly	Leukocyte Count	Important Laboratory and Special Examinations	Discussed on Page
Brucellosis	Rg, R, or Ir	Rare	Occasional	Frequent	Low or normal	Blood culture, agglutination test, intracutaneous test	93
Influenza	Rg or Ir	None	None	None	Low or normal	Inoculation of nasopharyngeal washings into mouse, ferret or chick embryo	
Malaria	In or Ir	None	None	Frequent	Low	Blood film	
Miliary tuberculosis	Ir or Rg	None	Occasional	Frequent	Low, normal, or slightly or moderately elevated	Sputum examination for tubercle bacilli, X-ray of lungs, culture or guinea pig inoculation of other material if accessible	312
Salmonella fever (including paratyphoid fever)	Rg, Ir	Frequent	None	Frequent	Low or normal	Culture of blood and stools, agglutination test	74
Trichinosis	R, Ir	Rare	None	None	Slightly or moderately elevated	Intracutaneous test, biopsy of muscle, differential blood count	
Tularemia (typhoidal form)	I, R, Rg	Occasional	Occasional	Rare	Normal or slightly elevated	Agglutination test. Inoculation of guinea pigs with blood or material from local lesions or regional node	366
Typhoid fever	Rg, Ir	Frequent	None	Frequent	Low or normal	Culture of blood and stools, agglutination test	253

Group II Diseases Having Clinical Features Pointing to One Organ or Part Which Are Frequently Overlooked in the Presence of the Evidences of Generalized Infection

Name	Type of Fever*	Rash	General Lymphadenopathy	Splenomegaly	Leukocyte Count	Important Laboratory and Special Examinations	Discussed on Page
Abscesses: hepatic, pelvic, perinephric, retroperitoneal, subdiaphragmatic and others	Ir, Rg	None	None	None	Slightly, moderately elevated	Culture of abscess, if accessible. Blood culture	‡
Bacteremia	Ir or Rg	Occasional	Rare	Occasional	Elevated	Repeated blood cultures	‡
Cholecystitis (intermittent biliary obstruction)	I	None	None	None	Elevated or normal	Examination of duodenal contents	
Encephalitis	I or Rg	None	None	None	Normal or slightly elevated	Examination of cerebrospinal fluid	
Endocarditis	I or Rg	Frequent	Rare	Frequent	Normal or elevated	Repeated blood cultures	1 3
Infectious mononucleosis	Ir or Rg	Occasional	Frequent	Frequent	Elevated or normal	Agglutination test for heterophile antibody, differential blood count	
Meningitis	Rg or I	Frequent	None	Rare	Elevated	Examination of cerebrospinal fluid, blood culture	‡
Osteomyelitis	I, Rg	None	None	None	Elevated	Blood culture, X-ray	193
Otitis media	I or Rg	None	None	None	Elevated or normal	Cultures from middle ear and pharynx	‡
Pericarditis	I, Rg	None	None	None	Elevated or normal	Blood culture, electrocardiogram, fluoroscopy	‡
Prostatitis	I	None	None	None	Usually normal	Microscopic examination and culture of prostatic fluid	
Rat bite fever	I, R, In	Frequent	Occasional	Infrequent	Slightly or moderately elevated	Blood culture, inoculation of [illegible] guinea pigs	432
Salpingitis	I or Rg	None	None	None	Elevated	Culture from cervix, blood culture	‡
Sinusitis, acute purulent	Ir	None	None	None	Slightly elevated or normal	Culture of material from sinuses	
Syphilis, secondary and late	Ir or Rg	Frequent	Frequent	Rare	Normal	Complement fixation or flocculation test	
Thrombophlebitis	I or Rg	None	None	None	Normal, elevated or moderately elevated	[illegible]ogram, blood culture	
Tuberculosis of bones, intestines, lungs, peritoneum and other organs	I or Rg	None	None	Occasional	Normal	Culture, guinea pig inoculation of material, if accessible. Tuberculin test, X-ray	

Group III Diseases Infrequently Encountered in the Temperate Zones

Scrub typhus		+				+	Trunk then general	
Trench fever		+					Trunk	
Rickettsial pox				+			General	
Dengue fever	+	+					General	
Foot and mouth disease				+			Face hands feet	
Erysipeloid	+						Hands	Extremities face
Sporotrichosis			+				Extremities	General
Leprosy		+	+				Extremities face exposed skin	Anywhere
Yaws		+					Face extremities	
Plague						+	General	
Glanders			+				Extremities	

Group IV Diseases Which May Be Infectious or Related to Infection

Pityriasis rosea		+					Trunk	
Erythema multiforme		+		±†			Face and extremities later general	
Erythema nodosum			+				Extremities	
Lupus erythematosus		+	±	±			Face and extremities	General
Periarteritis nodosa		+	±			±	Anywhere	
Boeck's sarcoid			+				Anywhere	

TABLE [illegible]

CLASSIFICATION OF DISEASES ACCORDING TO THE CHARACTER OF THE ERUPTION WHICH ACCOMPANIES THEM

Group I Diseases Occurring Particularly in Children

Disease	Type of Eruption						Location of Rash	
	Erythematous	Maculopapular	Nodular	Vesicopustular	Pustular	Petechial or Hemorrhagic	Commonest	Others
Measles		+					Face then general	
Rubella (German measles)		+					Face then general	
Scarlet fever	+						General	
Chickenpox				+			Trunk then general	
Impetigo contagiosa and staphylo[illegible]				+			Anywhere	
Roseola infantum		+					Extremities then general	

Group II Diseases Occurring in Adults or in Patients of All Ages

Disease	Erythematous	Maculopapular	Nodular	Vesicopustular	Pustular	Petechial or Hemorrhagic	Commonest	Others
Syphilis		+		±			General	
Typhoid and Salmonella fevers		+				±	Trunk	Extremities
Erysipelas	+						Face	Extremities anywhere
Furunculosis					+		Anywhere	
Meningococcic infections		+				+	Extremities and trunk	General
Bacterial endocarditis			±			+	Anywhere	Extremities (nodules)
Bacteremias						+	Anywhere	
Rocky Mountain spotted fever		+				+	Extremities then general	
Typhus fever		+				+	Trunk then extremities	Rarely involves face hands or feet
Smallpox				+		±	Face trunk then general	
Rat bite fever	±	+				±	Extremities then general	
Herpes simplex				+			Face	Anywhere
Herpes zoster				+			Trunk	Anywhere

Croup III Di eases Infrequently I ncountered in the Temperate Zones

Scrub typhus		+				+	Trunk then general	
Tr nch fever		+					Trunk	
Rickettsial pox				+			Cen ral	
Dengue fever	+	+					General	
Foot and mouth di e se				+			Face hands fe t	
Ery ipelo d	+						Han ls	Extremities face
Sporotrichosis			+				Extremities	General
Leprosy		+	+				Extremities fr exposed kin	Anywl re
Yaws		+					Face extremiti s	
Plague						+	Cen ral	
Clanders			+				Extremiti s	

Croup IV Dise ses Which May Be Infectious r Related to Infection

Pityria is ro ea		+					Trunk	
Erythema multiforme		+		±†			Face and extremities later general	
Erythema nodosum			+				Extremities	
Lupus erythematosus		+	±	±			Face and extremities	General
Periarteritis nodosa		+	±			±	Anywhere	
Boeck s sarcoid			+				Anywhere	

TABLE 2—*Continued*

Group V Noninfectious Diseases Which Cause Confusion in Diagnosis

Disease	*Type of Eruption*						*Location of Rash*	
	Erythematous	Maculopapular	Nodular	Vesicopustular	Pustular	Petechial or Hemorrhagic	Commonest	Others
Leukemia		±			±	+	Anywhere	
Hodgkin's disease			+				Face and extremities	
Purpuras (all types)						+	Anywhere	
Dermatitis medicamentosa	+	+		+			Extremities	
Dermatitis venenata	+	+		±		±	General	Anywhere

The rash of scarlet fever is an erythema plus miliary follicular papules

† Vesiculobullous

Low grade fever is the term usually used to describe fever which does not go above 102 F

Irregular fever is the term applied to any type of fever which does not fit into the above categories

ETIOLOGY OF FEVERS

In addition to infections other physiologic and pathologic conditions may be accompanied by fever as follows

1 **The Absorption of Proteins** These may be foreign proteins such as injected milk or typhoid vaccine or they may be proteins from the patient s own tissues as in the absorption which follows burns or surgery The fever which accompanies neoplasms and the low grade fever which is frequently present when pneumonia is resolving, probably belong in this category

2 **Dehydration** The reduction in body water prevents proper dissipation of heat from the body

3 **Drugs** Caffein and epinephrine are examples of drugs capable of causing fever

4 **Hypersensitivity** This may result from chemical substances serums or antibiotics

5 **Metabolic and Endocrinologic Disorders** Hyperthyroidism is the most common example of this

6 **Physical Factors** Examples are heat stroke and artificial fever induced for therapeutic purposes

7 **Psychogenic Factors** Tension states will often result in slight increases in temperature

8 **Neurogenic Factors** Injuries to certain nerve centers will cause fever These are encountered so infrequently as to be relatively unimportant clinically

9 **Fictitious Fever** This occurs when a malingerer alters the thermometer to give the impression that he has fever

CLASSIFICATION OF FEVERS DUE TO INFECTIONS

Table 1 lists the infections in which fever is the outstanding sign The diseases in Group I are almost always characterized by general symptoms alone Even when localizing signs are present they are rarely diagnostic Laboratory and special examinations must usually be depended upon to make the diagnosis

The infections listed in Group II are either localized or have distinguishing clinical features in a majority of instances but these signs may be absent or may be easily overlooked In such cases the infection may be confused with the diseases in the other groups The diseases listed in Group III resemble those in Group II except that the distinguishing features are often absent early in the disease and are detected only after one or more days have passed

Several diseases of noninfectious or of unknown etiology have been placed in Group IV Here again the localizing or distinguishing signs may be absent or easily overlooked and fever may be the only evident clinical feature

Diseases Characterized by an Eruption

Many of the infectious diseases display an eruption as a prominent feature In others an eruption is present in a certain proportion of cases Table 2 lists the infectious diseases characterized by a rash The type of rash which is commonly observed is indicated by a plus sign while the types of rash which are less frequently seen are indicated by plus minus signs The infectious diseases which are more commonly observed in the United States are tabulated in Groups I and II while the rarer conditions have been placed in Group III Groups IV and V contain the diseases of doubtful and of noninfectious etiology respectively which may be confused with infectious diseases because they sometimes exhibit similar eruptions

Diseases Characterized by Pharyngitis

The infectious diseases in which an acute pharyngitis is a prominent symptom are listed in Table 3 together with some of the outstanding features of the pharyngitis and the laboratory tests which are of value in the differential diagnosis Special attention is called to the noninfectious diseases which may display throat lesions that simulate acute infections of the pharynx

Infectious Diseases Associated with Pulmonary Infiltration

The differential diagnosis of these conditions is given under pneumococcic pneumonia on pages 110 to 115

Bacterial Infections of the Meninges

Whenever an infectious disease is accompanied by symptoms of central nervous system involvement (headache vomiting paralyses of nerves stupor coma convulsions or disorientation) or by signs of meningeal involvement (nuchal rigidity or a positive Brudzinski or Kernig sign) a lumbar puncture should be performed The differential diagnosis between infectious and noninfectious conditions affecting the meninges and among the various infectious types of meningitis can usually be made from the examination of the fluid obtained

When the central nervous system and meninges have not been infected but are presumably only irritated by toxins the condition is called meningismus Under these circumstances the cerebrospinal fluid will be normal except for an increase in pressure and occasionally a slight increase in lymphocytes

TABLE 3

DISEASES CHARACTERIZED BY PHARYNGITIS

Disease	Clinical Features			Laboratory Examinations	Discussed on Page
	Color	Exudate or Membrane	General Symptoms		
Streptococcic sore throat	Fiery red	White easily wiped off	High fever marked toxicity vomiting Rash in scarlet fever	Culture for beta hemolytic streptococci	136
Unclassified respiratory infections	All degrees of redness	Usually scant or absent Wiped off easily	Temperature and toxicity often slight or moderate	No specific organisms on culture	
Diphtheria	Dull or purplish red	Gray removed with difficulty leaving bleeding points	Fever low pulse rate high and lassitude great if infection is severe	Microscopic examination and culture for diphtheria bacilli	381
Vincent's angina	Inflammation confined to area about membranes	Friable with foul odor Leaves dirty base when removed	Fever and constitutional symptoms mild	Stain smear for Vincent's organisms	
Infectious mononucleosis	Dull red	White or gray absent slight or extensive Usually pulled off easily	Fever and constitutional symptoms mild or severe Generalized lymphadenopathy	No specific organisms on culture Typical early lymphocytes in blood smear Positive heterophile antibody test	
Syphilis	Dull red	None Mucous patches usually present	Fever and constitutional signs usually mild General lymphadenopathy	*Dark field examination from primary* lesion or mucous patches Serologic test for syphilis	
Thrush	Inflammation slight	Large white friable removed with difficulty leaving bleeding surface	Mild	Smears and cultures will demonstrate *Oidium albicans*	
Noninfectious diseases characterized by pharyngitis					
Leukemia	Variable	Variable	Prostration and weakness	Leukocyte count or biopsy as indicated	
Agranulocytosis and aplastic anemia	Variable	Variable	Prostration and weakness	Leukocyte count or biopsy as indicated	
Neoplasms	Variable	Variable	Prostration and weakness	Leukocyte count or biopsy as indicated	

TABLE 4

Typical Cerebrospinal Fluid Findings in Diseases of the Central Nervous System

	Pressure	Cellular Elements		Chemical Elements			Other Cerebrospinal Fluid Examinations	Other Examinations	Discussed on Page
		Lymphocytes	Polymorphonuclears	Dextrose	Protein	Chlorides			
Normal values	100 to 200 mm. of water	0–9 per cu. mm.	0	45 to 65 mg. per 100 cc.	15 to 40 mg. per 100 cc.	6[illegible]0 to 7[illegible]0 mg. per 100 cc.			
Virus infections	N or I‡	I	N†	N	I	N	Animal inoculation	Test of serum for development of antibody	
Tuberculous and Torula meningitis	I	I	N or I	L	I	L	Smear, culture and Guinea pig inoculation for tuberculosis; [illegible]	Examination of sputum for tubercle bacilli	3[illegible]3
Other bacterial meningitides—mild	I or N	N	I	N	I	N	Smear, direct typing and culture	Blood culture	203
Other bacterial meningitides—moderate or severe	I or N	N	I	L	I	L	Smear, direct typing and culture	Blood culture	203
Syphilitic meningitis	I or N	I	N	N	I	N	Serological test for syphilis, colloidal gold curve	Blood serological test for syphilis	
Abscess of brain or lateral sinus thrombosis	N or I	I	N or I	N or I	N or I	N	Culture	Blood culture. Culture from middle ear or sinus if infection is present	
Tumor of brain	N or I	N or I	N	N	N or I	N		Encephalogram, arteriogram	

* Usually less than 1000 per cu. mm.
† Polymorphonuclears often increased early in equine encephalomyelitis and poliomyelitis.
‡ N = within normal limits, I = increased above normal limits, L = lowered below normal limits.

When the meninges are irritated by the presence of red blood cells as in subarachnoid or subdural hemorrhage the pressure may be increased and the fluid will be uniformly bloody After centrifugation the *supernatant will be xanthochromic unless the lumbar puncture has been* done within a few hours after the onset of the hemorrhage Aside from

TABLE 3

INFECTIOUS DISEASES ASSOCIATED WITH ARTHRITIS AND CONDITIONS WHICH MUST BE DIFFERENTIATED FROM THEM

	Diagnostic Procedures	*Discussed on Page*
Bacterial arthritis du to		
Gonococci	Culture of urethral or cervical discharge	22
Pneumococci	Typing of sputum culture of blood	131
Staphylococci	Culture of infectious foci and blood	198
Streptococci	Culture of infectious foci and blood	14?
Meningococcemia and meningococcic meningitis	Culture of spinal fluid and blood	?03
Brucellosis	Blood culture agglutination and intradermal tests	?93
Streptobacillus moniliformis infections	Blood culture	43?
Spirillum minus infection	Mouse or guinea pig inoculation	133
Shigella dysentery	Culture of stools	280
Tuberculosis involving the joints	Culture and guinea pig inoculation from foci which may be tuberculous	
Syphilis involving the joints	Serological test for syphilis	
Reiter s Syndrome	Clinical features	?41
Acute rheumatic fever	Electrocardiograms	163
Acute rheumatoid arthritis	Roentgenograms of affected joints	
Serum sickness	History and clinical features	9
Sickle cell anemia	Examination of red blood cells for sickling x rays of bones	
Osteomyelitis	X rays of bones	193
Gout	X rays of joints blood uric acid	
Diseases of the synovium	X rays of joints biopsy	
Hemarthrosis du to		
(1) Disturbances in blood coagulation such as hemophilia pseudohemophilia prothrombin deficiency	Coagulation bleeding and prothrombin times platelet count tourniquet test vitamin C determination	
(2) Blood dyscrasias associated with thrombocytopenia or increased capillary fragility such as the purpuras aplastic *anemia leukemia and scurvy*	Coagulation bleeding and prothrombin times platelet count tourniquet test vitamin C determination	

In all cases where an infectious arthritis is suspected the synovial fluid should be cultured if any can be obtained and blood cultures should always be taken

the fact that the protein content will be increased the other spinal fluid values will be normal and no bacteria will be found unless there is an associated infection

If an inflammatory process of the brain or meninges is present the cerebrospinal fluid will exhibit the features shown in Table 4 The table

is self explanatory although it may be well to point out that occasionally when a lumbar puncture is done early in the course of a disease the typical changes may not yet have occurred Almost invariably if the examination is repeated within a day or two the characteristic features will be present

The recommended methods of examining the spinal fluid for the presence of bacteria are given in Figure 31 on page 208

Infectious Diseases with Associated Arthritis

In certain diseases the joints seem to be favored sites for attack This is particularly true in the infections caused by gonococci and meningococci (Table 5) Purulent arthritis is sometimes produced by other bacteria especially when there is an overwhelming infection Pneumococci staphylococci and streptococci belong in this group Other infectious diseases affect the joints less frequently Reiter s syndrome is a condition which closely simulates a gonococcic infection since both diseases may affect the urethra the joints and the eyes The etiologic agent is probably an organism in the pleuropneumonia group of bacteria Scurvy and osteomyelitis are usually distinguished from arthritis as a result of a careful physical examination since both these processes are in bones adjacent to the joints and not in the joints themselves Arthropathy may be a feature of hypersensitiveness to other substances as well as to serum The list includes several agents used in the treatment of infectious diseases such as the sulfonamides (particularly sulfathiazole) penicillin and streptomycin

2 *General Measures in the Treatment of Infectious Diseases*

Certain measures are useful in the treatment of many different infectious diseases regardless of their etiology These will be discussed in the present chapter in order to avoid repetition under the head of each individual disease

Rest

During a febrile disease the pulse rate the cardiac output and the oxygen consumption increase These changes reflect the increased amount of work done by the heart and other organs Physical rest by decreasing the work of the skeletal muscles permits the metabolism of other organs to be increased as demanded by fever The more severe the disease the higher the fever and the more marked the prostration the more important it is to conserve the strength by rest Accordingly in the severe infections rest should be complete bed rest without bathroom privileges and if possible with a nurse in attendance who anticipates the needs of the patient and substitutes her muscular activity for his wherever possible

In fever of a week s duration or less it is sufficient to keep the patient in bed until his temperature has been 98 6° F or below for twenty four hours after which he may be allowed to resume complete activity over the next week or two If the course of the fever is longer the number of days which the patient with normal temperature should spend in bed before activity is permitted is proportionately increased A simple rule is to increase this by one day for each week of fever

Bed rest is not an unmitigated blessing Certain harmful eventualities may take place in a patient kept in bed because of an infectious disease as well as for other diseases These have been described in detail by Harrison[5] and Powers[6] One of them is the formation of thrombi in the veins of the calf or thigh Fragments breaking off from these thrombi produce pulmonary infarction which may be fatal Second if there is any tendency toward the development of congestive heart failure edema of the lungs is more likely to occur if the patient is in the recumbent position A frequent sequel of this change in hydrodynamics is hypostatic pneumonia Third atrophy of the muscles and demineralization of the bones occur after prolonged periods of rest Fourth the digestive system tends to function poorly in the bedridden patient The most common clinical manifestation of this is abdominal distention The ever present

is self explanatory although it may be well to point out that occasionally when a lumbar puncture is done early in the course of a disease the typical changes may not yet have occurred Almost invariably if the examination is repeated within a day or two the characteristic features will be present

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Treatment of Fever

The rise in temperature which occurs as a result of infectious processes is preceded except in the case of a very slight elevation by the chilling process manifested either by chilly sensations or by an actual shaking chill During this stage treatment should be directed toward increasing the body heat by means of blankets hot water bottles and electric pads and by the administration of hot fluids

When the chilly stage is over the patient feels hot and may begin to perspire At this time only enough bedclothes should be used to keep the patient comfortable The pounding headache which is often present may be relieved by the application of cold or may require analgesic drugs During defervescence care must be taken that the patient s clothing is changed when it is wet with sweat so that he may not become chilled

Support of the Circulation

In severe infections a shocklike state supervenes similar in appearance to that observed in patients in shock following trauma or hemorrhage Once this condition has reached a severe stage as evidenced especially by depression of the systolic and diastolic blood pressures little can be done directly to alter it It is the physician s task to prevent its occurrence by the prompt use of specific measures (such as serums sulfonamides or antibiotics) to combat the infection If the patient has already entered the shocklike stage every attempt should be made to support the circulation long enough to allow the specific agents to clear up the infection and thus reduce the toxicity In order to do this plasma may be given intravenously always at a slow rate and always with care not to cause further embarrassment of the circulation Pressor drugs such as epinephrine neosynephrine and paredrine should be given at the same time Oxygen should also be administered as outlined below

Oxygen Therapy

In many infectious diseases the patient will benefit from the administration of oxygen This is particularly true in the pneumonias where there is often insufficient exchange of oxygen from the inspired air to the blood because of the operation of one or several of the following factors (1) Bronchi may be occluded thus preventing the ingress of air (2) alveoli may be crammed with bacteria leukocytes and erythrocytes (3) the blood vessels to the affected area may be closed (4) edema may be present in alveoli around the pneumonic area (5) when shallow respiration is present the air in the air passages may be replaced with fresh air while the alveolar air may be only partly replaced

Since these abnormalities are present to some extent in every patient with pneumonia the clinician should be on the alert to detect the first evidences of oxygen want While cyanosis is the most common of these its presence must not be relied upon to diagnose anoxemia Cyanosis

possibility of one of these harmful effects should impel the physician to allow patients convalescent from infectious diseases to begin getting out of bed as soon as possible and to encourage those who must remain in bed to move about as freely as their condition will permit

Diet

Patients with infections usually lose more nitrogen than they take in thus depleting their store of proteins In acute infectious diseases this has been found to occur in spite of high caloric and high protein intakes as shown by Grossman [4] On the other hand Coleman[3] was able to prevent the loss of weight which usually occurs during the relatively long course of typhoid fever by the use of high caloric diets During the course of a short infectious disease it is not necessary to coax the patient to eat provided that he takes a sufficient amount of fluids During convalescence he should be given a high protein high caloric diet and encouraged to eat it all When the illness from which the patient suffers is likely to be prolonged a diet rich in protein and in calories should be given from the start When the patient is obviously not taking enough food by mouth oral feeding may be substituted by the intravenous injection of dextrose and of protein hydrolyzates such as amigen or by mixtures of amino acids as described in the chapter on typhoid fever (see p 270)

Treatment of Anemia

During infections an anemia sometimes develops Beyond the fact that it is normochromic or sometimes slightly hypochromic little is known concerning its development and the reasons therefor It responds to iron poorly or not at all If anemia is severe transfusions or suspensions of red blood cells should be given Otherwise treatment may be postponed until convalescence when iron should be given

Fluids

Whether the patient s intake of food is adequate or not it is important that he receive a sufficient amount of fluids for several reasons Since the majority of the physiologic mechanisms in the body are dependent upon water for their action it is imperative that water be supplied for use in the ordinary functions of the body plus the additional amount needed to take care of the increased activities and evaporation incident to the infection When fluids are scanty bladder irritation is likely to occur and any tendency to constipation is increased The increased tissue breakdown which occurs during fever produces an increase in nitrogenous waste substances If sufficient water cannot be spared to transport this nonprotein nitrogen accumulates in the blood Whenever sulfonamides are being administered it is necessary that enough urine be excreted to prevent precipitation of the drugs in the urinary tract and the consequent formation of calculi (see p 51)

should be withdrawn slightly and held in this place by adhesive tape on the outside of the nose The catheter should be cleaned and replaced whenever it gets clogged with secretions Oxygen for the catheter must be bubbled through water to humidify it (Fig 1) According to Barach[2] the concentration of oxygen in the inspired air when this method is used varies in the average adult from 33 per cent when the flow is 4 liters per minute to 42 per cent at 8 liters per minute The same author states that concentrations of oxygen in the inspired air of 45 per cent or more can be obtained at a flow of 6 liters per minute if the free end of the catheter is placed in the oropharynx instead of the nasopharynx This is

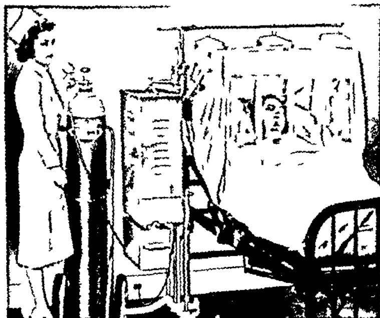


Fig 2 Oxygen tent (Courtesy of Ohio Chemical and Manufacturing Company)

done by inserting the catheter until the patient begins to swallow air then withdrawing it a short distance and fastening it with adhesive

CLOSED TENT The practical method which delivers high concentrations and at the same time provides controlled temperature and humidity is the oxygen tent *In this method there is placed at the patient s bedside* a portable cabinet which cools and humidifies the oxygen Attached to the cabinet is a canopy which fits over the upper part of the patient s body (Fig 2) A completely transparent tent is best since it helps eliminate the impression of confinement which patients often experience The ends of the tent should be snugly tucked in under the mattress and under a sheet stretched tightly across the patient s thighs to prevent leakage of oxygen The tent should not be opened any more than is

occurs when there is a sufficient amount of reduced hemoglobin in the peripheral blood to give the characteristic blue color If anemia is present *the total amount of hemoglobin will be so small that there will not be* enough of the reduced variety to cause the color Likewise if the patient is in shock the surface vessels will be so contracted that there will not be enough blood under the skin to give it a blue color Other signs of anoxemia which may appear before cyanosis are a rapid pulse rate rapid respiration unexplained by the pathological process or undue restlessness

Another condition requiring oxygen is that of peripheral vascular failure or medical shock which is seen in overwhelming infections caused

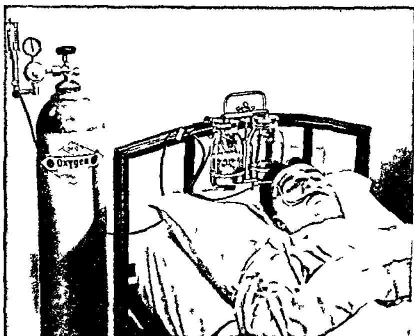


Fig 1 Oropharyngeal catheter outfit (Courtesy of Ohio Chemical and Manufacturing Company)

by various infectious agents The clinical features of this syndrome have been given in the preceding section

Whatever the condition for which oxygen is required it should be given promptly and should be continued until there is no longer any need for it

Methods of Administration NASAL CATHETER The simplest of the efficient methods of administering oxygen is by a catheter inserted into the nasopharynx or oropharynx The last inch of a size number 10 (French) catheter should be perforated with three to six holes at different points on its circumference It is then lubricated and passed through one of the patient s nostrils When it is felt to touch the back wall it

should be withdrawn slightly and held in this place by adhesive tape on the outside of the nose The catheter should be cleaned and replaced whenever it gets clogged with secretions Oxygen for the catheter must be bubbled through water to humidify it (Fig 1) According to Barach[2] the concentration of oxygen in the inspired air when this method is used varies in the average adult from 33 per cent when the flow is 4 liters per minute to 42 per cent at 8 liters per minute The same author states that concentrations of oxygen in the inspired air of 45 per cent or more can be obtained at a flow of 6 liters per minute if the free end of the catheter is placed in the oropharynx instead of the nasopharynx This is

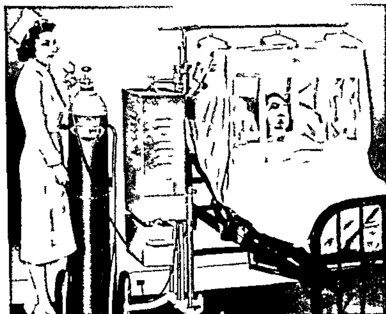


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absolutely necessary Most of the patient s needs can be attended to through the flaps in the tent provided for that purpose The oxygen content should be tested at least twice a day and preferably oftener if the tent has been removed frequently These tents when used properly will deliver oxygen in concentrations of from 40 to 60 per cent and even higher Used improperly they may often contain no more oxygen than the air of the surrounding room

OPEN TOP TENT The open top tent is shaped like a box without a top or bottom This is placed over the patient s head and neck and connected with an oxygen tank and regulatory valves A high concentration of



Fig 3 B L B inhalation apparatus with nasal mask (Courtesy of Ohio Chemical and Manufacturing Company)

oxygen (about 50 per cent) will build up at the level of the patient s nose *when a flow of about 6 liters of oxygen per minute is coming into* the tent because only small amounts of the gas will escape through the open top This apparatus works well for infants and small children and is simple to operate It should be guarded from drafts which blowing across the open top will suck oxygen out more rapidly than it can be replaced

OXYGEN MASKS The most exact control over the concentration of oxygen and the highest concentrations of the gas may be obtained by the use of special masks The B L B mask (devised by Boothby Lovelace and Bulbulian) (Fig 3) is equipped with a rebreathing bag and will

deliver oxygen to an adult of average size in concentrations varying from 60 per cent at a flow of 4 liters per minute to 100 per cent at a flow of 7 to 8 liters per minute The meter mask (invented by Barach and Eckman) is equipped with a bag which does not collect expired air but only the inflowing oxygen which accumulates while the patient is exhaling This mask provides 100 per cent oxygen when the system is completely closed or may be regulated so that the oxygen as it flows in from the tank will suck in a prearranged amount of outside air It has the advantage that it may be adjusted to deliver exact concentrations of oxygen all the way up to 100 per cent with the accompaniment of minimal amounts of carbon dioxide It may also be metered so as to cause the patient to exhale under positive pressure This device is extremely useful and may be life saving in a patient with pulmonary edema

Other methods of administering oxygen are by double-pronged tubes which fit into the nostrils by face tents or loose fitting masks and oxygen chambers or rooms Tubes which fit in the nostrils are not recommended because only relatively low concentrations of oxygen can be delivered in this way and because they become displaced easily and are useless if the patient chooses to breathe through his mouth Face tents and loose fitting face masks are not recommended since they are difficult to adjust because the exact amount of oxygen delivered cannot be calculated and uncomfortably large amounts of moisture and carbon dioxide may collect within them unless the proper oxygen flow is continued Special rooms equipped to contain regulated concentrations of oxygen under conditions of proper humidity and temperature and large enough to admit one or more patients together with their attendants constitute an ideal method of administering oxygen but are available in only a few hospitals

A special hood has been devised for the administration of helium oxygen mixture which allows efficient control of the concentrations of these gases administered under positive pressure

The advantages and disadvantages of the recommended methods of oxygen administration are summarized in Table 6 In general it may be said that for young children and infants the open top tent is preferable Most adults will do well with the catheter or the closed tent method while face masks are usually employed for patients who require high concentrations of oxygen or where exact regulation or the use of positive pressure is important It cannot be stressed too strongly that the mere employment of one or the other type of apparatus does not guarantee efficiency Any method will be worse than useless if it is used improperly whereas even a type which has outstanding disadvantages will contribute materially to the care and comfort of the patient if the attendant understands its use and watches it carefully while it is in operation

STERILIZATION OF OXYGEN APPARATUS Since bacteria may lodge at any place contacted by the air exhaled by the patient it is important that the apparatus be sterilized before it is used again Catheters of

course are most easily sterilized since they may be boiled Tents should be washed inside and out with soap and water after which 70 per cent alcohol should be applied to the entire inside surfaces except plastic windows which would be clouded by the use of alcohol Rubber parts

TABLE 6

ADVANTAGES AND DISADVANTAGES OF THE PRACTICAL METHODS OF ADMINISTERING OXYGEN

Method	*Advantages*	*Disadvantages*
Nasopharyngeal or oropharyngeal catheter	(1) Simple and economical (2) If properly placed causes little annoyance to the patient (3) Easiest to sterilize	(1) Very high concentrations cannot be delivered (2) May be uncomfortable or inefficient if not properly placed (3) Not suitable for young children
Closed tent	(1) Provides comfortable environment as well as adequate concentrations of oxygen	(1) Initial cost high (2) Delirious patients sometimes become maniacal probably because of feeling of confinement (3) Oxygen content becomes low if not kept properly closed (4) Requires frequent testing of oxygen concentration
Open tent	(1) Most practical apparatus for young children and infants	(1) Cannot be relied upon to give proper concentrations of oxygen and carbon dioxide when used by adults (2) Requires frequent testing of oxygen concentration
Tight fitting face masks (B L B and meter masks)	(1) Exact concentrations of oxygen can be delivered (2) Higher concentrations can be given than with any other method (3) Positive pressure may be maintained by the meter mask	(1) Often annoying to the patient

of masks should be washed and boiled for ten minutes and the metal parts should be washed thoroughly with soap and water and placed in a chemical antiseptic for the proper length of time

ISOLATION PROCEDURES

When patients are ill with a bacterial disease certain of their secretions excretions or discharges will contain infectious agents which may be conveyed to other persons either directly or indirectly through the medium of the personnel in attendance or by means of contaminated articles In order to prevent the spread of the disease such patients

should be isolated, that is, separated for the period of communicability from everyone except those needed to attend them. The attendants in turn are required to observe precautions which will prevent the direct or indirect spread of the infectious agent to themselves or to other persons. A further benefit of isolation is that it often protects the patient from secondary infections which might otherwise be brought to him by other persons.

Laws and regulations for the control of infectious diseases vary in different localities concerning the diseases for which patients should be isolated. The physician in charge of the patient, however, may decide upon isolation procedures in other diseases, such as the common cold and influenza, even when local health department regulations do not require it.

Isolation Technique in the Hospital. The patient should be placed in a room or cubicle by himself or in a ward along with other patients suffering from the same disease. If this is not possible, he may be placed in a ward with patients having other diseases, but at a sufficient distance so that cross infection will not occur. Thereafter, until the patient's period of infectiousness is over and he is released from isolation, those who attend the patient must wear a mask and gown when in the patient's room or in his vicinity, if he is in a ward, in order to prevent contamination of their clothes. Attendants must thoroughly scrub their hands or any part of their body which has touched the patient or the contaminated area (for instance, the attendant's face if the patient should cough or sneeze directly into it). The mask and gown should be discarded before the attendant visits the next patient. Contaminated instruments should be boiled or wiped with 70 per cent ethyl alcohol or sterilized in some other way. The specific methods of carrying out the above procedures will vary *in different hospitals. If physicians, nurses and other* attendants understand the principle involved, they can readily learn the technique employed in any given place.

Isolation Technique in the Home. Isolation procedures are more difficult to carry out in the home than in the hospital, both because of the lack of proper facilities and because the attendants cannot be thoroughly trained in the aseptic technique in the limited time available. We agree with Anderson's[1] reasoning when he says: "To approach the problem not with the thought of achieving absolute asepsis but rather with the aim of reducing the chances of infection by concentrating on the main sources of spread and attempting to cut these down as much as possible seems the more logical course of action. Attention should be first directed to the chief mode of spread, then to the next most important channel, in each case instructions being given the attendant as to methods of minimizing the spread from this source."

General procedures to be applied when isolation of the patient is required are as follows:

1 The patient should be confined to a room or rooms for his or her exclusive use for the duration of the communicable period of the disease

2 With the exception of medical and nursing attendants no visitors *should be permitted during the isolation period*

3 The person giving nursing care should wear a gown or a large apron over her usual clothing when caring for the patient This gown should be left hanging near the door of the patient s room

4 After handling the patient or any articles used or touched by him the person giving nursing care should either wash her hands thoroughly *with soap and running water or immerse her hands in a disinfecting* solution and allow them to dry in the air

In the care of patients with pneumonia meningococcic meningitis tuberculosis diphtheria and infections with hemolytic streptococci the following additional procedures should be carried out

1 All discharges from the nose and throat should be destroyed by burning Clean cloths or paper tissues should be used and discarded into a paper bag which is then burned

2 Dishes and other eating or drinking utensils as well as food remnants should be dropped into a dishpan of soapy water in the patient s room This pan should be carried directly to the stove and the contents boiled for five minutes The dishes and utensils should be kept separate from those used by the rest of the family until the period of isolation is over

3 Linen from the patient s room should be dropped directly into a paper lined basket and carried directly to the laundry for immersion in hot suds and subsequent washing At the end of the isolation period the basket can be disposed of by burning

4 Other articles removed from the patient s room should be aired *cleansed with soap and water immersed in an antiseptic solution or* boiled according to the type of article

For patients with typhoid fever dysentery or various forms of diarrhea the following procedures should be carried out

1 All waste food and body wastes except stool and urine should be destroyed by burning

2 All dishes and other eating utensils should be treated as outlined in the previous section

3 Before stool urine or vomitus specimens are disposed of they should be treated with a disinfecting solution and allowed to stand for at least one-half hour Fecal masses should be broken up before treatment Chlorine in the form of chloride of lime or bleaching solutions is an effective disinfecting agent and is also a deodorizer

4 Linen removed *from the sickroom should be washed in hot soapy* water immediately and other articles should be cleansed aired or immersed in disinfecting solutions depending on the type of article

When the patient is released from isolation

1 He should be given a bath and clean clothes

2 The sickroom should be thoroughly cleaned hot water and soap being used wherever possible If possible the room should be aired for twenty four hours or more before being used again In any event use of the room should be avoided for at least six hours

3 All mattresses pillows blankets toys and books used by the patient should be aired for at least six hours in direct sunlight Mattresses blankets pillows and rugs may be dry cleaned if they require it

When there is a choice of attendants it is wise to let the burden fall on a person known to be immune (for instance in a case of diphtheria the attendant should be Schick negative if such a person is available) In the case of diseases for which immunization procedures are available such as typhoid fever the attendants should be vaccinated promptly

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When the patient is released from isolation

rendered entirely unnecessary by the sulfonamides penicillin streptomycin and other chemotherapeutic and antibiotic agents Antibacterial serums were formerly used extensively in pneumococcic pneumonia and meningococcic meningitis and less frequently in erysipelas bacillary dysentery anthrax tularemia and staphylococcic infections Antibacterial serum is still advised in severe cases of *H influenzae* meningitis This antiserum is produced from rabbits

2 Antitoxic serums or antitoxins are effective against the soluble exotoxins of bacteria Since the sulfonamides and the antibiotics which have been developed up to the present time are not effective against these toxins the antitoxic serums are just as important weapons in the physician s armamentarium as they ever were They are

Tetanus antiserum produced from horses or from cattle
Diphtheria antiserum produced from horses
Scarlet fever antiserum produced from horses
Gas gangrene antiserum produced from horses
Botulinus antiserum produced from horses

3 Serums against diseases which are not caused by bacteria include anti Rocky Mountain spotted fever serum antivenins and the gamma globulin fraction of human serum the latter used especially for the prevention or modification of the course of measles

Reactions to the Administration of Serum

Unfortunately when patients are given serum certain reactions may occur which although often mild are occasionally severe and sometimes fatal Since the prevention or amelioration of these reactions is an important objective in the proper administration of serum we shall consider first the characteristics of these reactions and the factors influencing them After this the technique of administration of serum will be discussed

Reactions to the administration of serum are of several kinds (1) thermal (2) anaphylactic (3) circulatory and (4) serum sickness

Thermal Reactions

It has long been known that injections of a foreign protein may cause fever The proteins contained in antiserums are no exception to this rule The most pronounced reactions are characterized by a severe rigor coming on at any time from a few minutes to an hour and a half after the injection of the serum or in intravenous injections sometimes beginning while the serum is still being administered The chill may last from a few minutes to an hour or more When the temperature is taken by rectum it is observed to rise progressively during the chill phase until at its height it may be as much as four or five degrees higher than it was before the serum was administered The rise in fever is in general proportional to the severity of the chill The elevation in temperature

3 Serum Therapy

An animal host usually responds to disease caused by bacteria by the production of antibodies. These substances aid the host in destroying or otherwise disposing of the infecting organisms. Antibodies are present, at least in the case of antipneumococcus serums, in the gamma globulin component of the animal's serum or in a component between the beta and gamma fractions. An animal will also develop a high titer of antibodies if it receives progressively increasing quantities of killed or living bacteria. If blood is taken from the animal thus immunized and the serum, or the portion of the serum containing the antibody, is administered to a new host, animal or human, it may (1) prevent the development of an infection by the micro-organism used for immunization, (2) insure that the disease which develops will be mild, or (3) bring about recovery in a case which would otherwise have been fatal.

While many animals have been used for the production of serums containing antibodies (antiserums), all the commonly used commercial antiserums are obtained from horses, rabbits or cattle. Serums from convalescent human patients have been used frequently in the treatment of certain diseases, and recently there has been a reawakening of interest in the employment of the gamma globulin from human serum.

Absorption of Serum

When antipneumococcic serum is administered intravenously, high titers of antibody are present in the blood immediately.[5] After intramuscular injection, the serum antibody reaches its peak in ten or more hours, whereas this point is not reached for twenty-four hours or longer when the serum is given subcutaneously. Since even a few hours may mean the difference between death or life in many patients with acute infectious diseases, the intravenous route is usually preferred.

When serum is administered by other routes, such as into the intrathecal space or into the peritoneal cavity or by the inhalation of finely atomized particles, absorption usually takes place into the systemic circulation in appreciable, although variable, amounts.

Kinds of Serum in Use at Present

The antiserums available at the present time for the treatment of bacterial diseases may be classified into two groups: (1) antibacterial serums and (2) antitoxic serums.

1. Antibacterial serums are effective against whole bacteria. They have been to a large extent displaced and probably will eventually be

reaction is mild the symptoms may subside gradually and the patient recover

Prevention Anaphylactic reactions will occur rarely if certain procedures are carried out before serum is administered The necessary precautions are discussed on page 33

Treatment Prompt recognition of an anaphylactic reaction is imperative since the proper treatment in order to be life saving may have to be initiated within a few seconds As will be emphasized later a bottle of epinephrine solution and a syringe and needle should always be on hand at the patient s bedside when serum is being administered At the first sign of an allergic reaction 0 5 to 1 0 cc of a 1 1000 solution of epinephrine hydrochloride should be administered intramuscularly and the site massaged vigorously in order to speed entry of the epinephrine into the circulation If the patient s condition requires more urgent action 0 3 cc of this solution should be given slowly into a vein If the veins are collapsed and death appears imminent the epinephrine may be given directly into the heart Injections of epinephrine should be repeated at intervals as required until the patient is completely free from danger or relapse This means that he must not be unattended for a moment during this time Prompt treatment at the beginning of an allergic reaction and careful attention for the succeeding hours are absolutely necessary

Circulatory or Shocklike Reactions

Rutstein[3] has studied another type of immediate reaction occurring particularly in older people which is characterized by circulatory changes such as rapid weak or irregular pulse profuse cold perspiration and a drop in blood pressure—in other words the signs of acute peripheral vascular collapse Death occurred in 31 9 per cent of the patients who were thus affected These reactions differ from anaphylactic reactions in that the incidence of patients with a history of allergy or of a positive cutaneous test for serum is not so high as that of patients with anaphylactic reactions

Treatment Epinephrine should be given immediately by intramuscular injection in doses of 0 5 to 1 0 cc and repeated at intervals as needed If the patient is *in extremis* epinephrine should be injected directly into the heart If the patient remains in a shocklike state he should be kept warm and oxygen should be administered

Serum Sickness

When serum is administered to persons who have never before received serum produced from a particular species of animal or who have not previously become sensitive to the proteins contained in the serum a significant proportion of these individuals will develop serum sickness This is thought to be caused by the formation of antibodies to some of the

caused by the administration of serum usually lasts for only a few hours Some patients do not have a definite rigor but experience only chilly sensations followed by fever while others feel warm and are found to have a temperature rise of a degree or two

Thermal reactions occur after administration of all kinds of serum They are much more frequent however when unconcentrated unrefined serums are employed and are observed less often when most of the inactive proteins have been removed They are much more likely to occur after the intravenous than after the intramuscular administration of serum Thermal reactions are not serious unless the patient s temperature is already elevated and the additional rise brings it to critical levels When rectal temperatures of 108° to 109° F are reached death is imminent unless prompt measures are instituted to reverse the trend

Treatment *During the chill phase the patient should be kept warm by blankets and hot water bottles These should be removed immediately when this phase is over so as to prevent further increase in the fever During the fever phase nothing need be done except to place an ice bag on the forehead and perhaps administer aspirin for comfort unless the temperature goes too high When the temperature rises to about 105° or 106° F tepid sponge baths alcohol baths or if necessary ice water enemas should be used to bring it down*

Anaphylactic Reactions

Persons who have natural (atopic) hypersensitiveness may be sensitive to the serum of any of the animals commonly used for the production of antiserums If they are injected with serum to which they are hypersensitive they may develop an *immediate serum reaction* which is classified as the *primary type* An individual who has received serum at some previous time may have been sensitized sufficiently so that he will develop a reaction to a subsequent injection If this occurs immediately it is known as an immediate serum reaction of the *secondary type* If it occurs later it is designated serum sickness and will be discussed under that heading

Clinical Features Within a few seconds to thirty minutes or more after the beginning of the injection the patient may experience a feeling of constriction in the chest of choking or of suffocation cough dyspnea or wheezing or any combination of these Itching of the eyes nose or throat and sneezing may be present Other symptoms which may occur alone or in combination with those just mentioned are itching or burning at the site of injection generalized urticaria edema of face and neck of the throat and larynx or of the extremities Abdominal pain vomiting diarrhea and restlessness often occur Other developments are pallor or cyanosis and a rapid weak pulse The blood pressure drops and a cold sweat appears The patient may become unconscious at the onset or after a few minutes or hours If prompt treatment is given or if the

more likely to be followed by an accelerated than by an immediate reaction

The symptoms and signs of serum sickness include the following fever rash edema lymphadenopathy arthralgia neuritis and other less frequent complications

Fever occurs in one-third to one-half of the patients with serum sickness In some patients it may be slight while in others the temperature goes as high as 103° to 105° F Confusion in diagnosis is often produced by the appearance of the fever from one to four days before the rash More commonly fever and rash start at the same time

The rash is urticarial in 80 per cent or more of the patients In the others it may be erythematous morbilliform petechial or purpuric although these types of rash appear more frequently in combination with urticaria than alone The rash lasts from twelve hours to four or more days

Edema is a common symptom with extremely variable clinical manifestations If the patient is carefully examined each day subcutaneous edema may be observed a day or two before the onset of the rash The area around the site of injection is most frequently involved and edema of the face is the next most common site Other subcutaneous areas may be affected or with more serious potentialities of danger the tongue pharynx larynx or esophagus Associated with the edema is a reduction in the excretion of chlorides often albuminuria and cylindruria occasionally reduction in the excretion of phenolsulfonephthalein and rarely suppression of urine

Lymphadenopathy is usually generalized and only infrequently localized in the area of the original injection The nodes are discrete and firm slightly or moderately tender and usually not greatly enlarged although occasionally they reach a diameter of several centimeters They do not return to normal size until several days to six weeks after the rash disappears

Arthralgia often occurs without any physical signs In a small proportion of patients redness and swelling of the joints occur and occasionally joint fluid may be increased to such an extent that it can be aspirated The fluid contains mostly lymphocytes with an occasional granulocyte

Involvement of the nervous system is manifested by a variety of syndromes The brain and spinal cord the meninges or the peripheral nerves may become edematous in the same way as the subcutaneous tissues or other organs Doyle[1] reviewing forty nine cases in which neurologic complications occurred found that the motor function was disturbed in all the patients and that about one-fourth had sensory changes in addition A neurological complication of serum sickness usually starts with severe neuralgic pains followed within a few hours to a few days by flaccid paralysis Pains in and tenderness of the muscles

serum proteins. These antibodies react with the serum protein which still remains in the body to cause the symptoms of serum sickness. This syndrome may appear as early as the third day after administration of the serum, although it is seldom observed before the sixth or seventh day.

Types of Serum Sickness. If the patient has previously been sensitized to the same protein, the period from the injection of the serum to the onset of symptoms may be shortened, in which case the disease is called an accelerated serum reaction. Or the symptoms may begin within a few minutes or a few hours after the serum is administered, in which event the syndrome is termed an immediate serum reaction. This latter condition is similar to the anaphylactic reaction already described; it carries the same hazards and should be treated in the same way.

Time of Onset. The onset of serum sickness occurred from five to ten days after the administration of the serum in 75 per cent of 1264 patients who developed this syndrome after the administration of horse serum.[2] In 96 per cent of the 1264 patients the symptoms began within fourteen days. The incubation period may rarely be as long as thirty days.

Incidence. The frequency with which serum sickness occurs varies greatly, depending upon the following factors:

1. The animal from which the serum is produced. The administration of horse serum results in more cases of serum sickness than the administration of rabbit serum. Serum from other animals is given so infrequently that the actual incidence of serum reactions cannot be determined.

2. The method of preparation of the serum. Concentrated and refined serum causes less serum sickness than unconcentrated serum.

3. The amount of serum administered. This is probably the most important single factor, since the incidence of serum sickness increases in direct proportion to the quantity of serum injected.

4. The route of administration. There is a difference of opinion as to whether serum sickness is more frequent after intravenous or intramuscular injections.

5. Race. Serum sickness is less frequently observed in Negro than in white patients.

6. Age and sex. These factors apparently play no part in the frequency of serum sickness.

7. Intervals between injections. This is an extremely important factor and must be considered with meticulous care whenever serum is given. In general it may be said that a second injection of serum within a week after the initial injection will have no effect upon the incidence and time of appearance of serum sickness. A second injection given from eight days to six months after the primary injection may be followed by an immediate anaphylactic reaction or by accelerated serum sickness. A second injection given later than six months after the first injection is

Local Serum Sickness In patients who have previously received serum and are later given an injection of serum derived from the same animal a gangrenous reaction may develop at the site of the original injection This resembles the Arthus phenomenon It is thought to be due to a local union of antigen and antibody The tissue destruction may be extensive and the period of convalescence prolonged for weeks or months In rare instances death has occurred The treatment is entirely symptomatic

Prevention of Serum Reactions—Measures Advocated for the Proper Administration of Serum

The dangers inherent in the use of serum may be minimized and deaths from serum accidents eliminated almost entirely if the proper procedures are carried out whenever serum is administered The steps which should be followed are shown in Figure 4

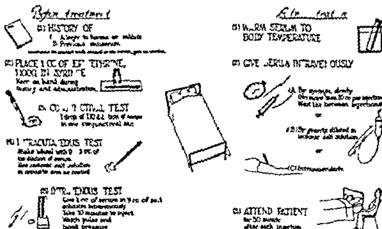


Fig 4 Procedures to be followed in administering antiserums.

BEFORE ADMINISTRATION OF SERUM

1 Careful inquiry should be made for a history of allergic conditions of all kinds The patient should be specifically questioned as to whether he has had contact with horses (or with rabbits if it is proposed to use serum from the latter animals) If there has been contact a careful inquiry should be made regarding the simultaneous occurrence of asthma allergic rhinitis urticaria or angioneurotic edema The patient should also be asked about previous injections of serum when and for what purpose they were given and whether there were any reactions after the administration of the serum

persist for weeks or even for months The muscles atrophy in long standing cases Most patients recover completely from the paralysis within six months although about 20 per cent are left with some weakness and atrophy The nerves associated with the brachial plexus are much more frequently involved than any others This is best explained by compression of these nerves by adjacent structures when edema is present Involvement of these nerves characteristically brings about atrophy of the supraspinatus infraspinatus and deltoid muscles

Other affections involving the nervous system are stupor convulsions hallucinations meningismus hemiplegia and paraplegia

Duration of Serum Sickness and Recurrence Kojis[3] found that in 88 per cent of his patients the symptoms lasted four days or less A duration of more than eight days was rare although some patients had the disease for periods up to eighteen days

In some instances the rash may return again after disappearing Repeated recurrences have been observed one patient having had as many as six altogether Recurrences result from the fact that antibodies to the different protein fractions of the serum appear at different time intervals after the injection of the serum Thus an individual may have an attack of serum sickness when antibodies to one fraction appear then after an interval of several days another attack when antibodies to a second fraction appear and so on

Treatment Urticaria will be relieved for short periods by the use of 0 3 to 0 6 cc of a 1 1000 solution of epinephrine Larger doses are seldom required and only serve to make the patient uncomfortable from the side effects Injections of 0 5 to 1 0 cc of a 1 500 solution of epinephrine in oil may be effective for as long as eight to twelve hours Benadryl or pyribenzamine in doses of 50 mg every two to three hours for adults and in proportionate amounts for children may be used instead and will often be effective We have not found ephedrine effective except in mild urticaria

State[4] observed that intravenous injections of procaine abolished or greatly relieved the symptoms of serum sickness For this purpose he recommended that 1 gm of procaine diluted in 500 cc of isotonic sodium chloride solution be given intravenously by the gravity method over a period of two hours A syringe containing amytal should be kept at the bedside for intravenous administration in case signs of procaine sensitivity should appear The procaine injections may produce temporary or permanent amelioration of symptoms If the relief is only temporary daily injections may be given

The itching may be alleviated by local application of calamine lotion containing 1 per cent phenol and by baths in water containing starch or sodium bicarbonate Arthralgia is often relieved by aspirin This drug may also lower the fever somewhat and relieve the headache and the other symptoms of malaise

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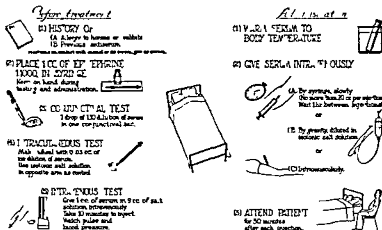


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appear within thirty minutes the dose may be doubled and this procedure may be repeated at thirty minute intervals until 1 cc of the undiluted serum is given If there is still no reaction the physician may go on to the next step in the procedure If a constitutional reaction such as the development of hives tightness in the chest asthma sneezing or rhinorrhea develops after any of the injections the attempt to give serum derived from the same animal should be abandoned In our opinion it is impossible to effect rapid desensitization of such a patient in order to make it safe to administer larger doses of serum

5 If the conjunctival and intracutaneous tests have been negative or if subcutaneous injections of the serum have produced no reactions 10 cc of a 1 10 dilution of the serum in isotonic sodium chloride solution should be given by vein at a rate not to exceed 1 cc per minute In order to insure slow injection a needle of small caliber should be used and a watch should be placed where it can be seen during the period of administration The pulse rate and blood pressure should be determined before the injection is started at intervals during the injection and for ten minutes afterwards A fall of twenty points in the systolic or ten points in the diastolic blood pressure or the development of anaphylactic symptoms contraindicates the administration of more serum derived from the same animal

Administration of Serum

1 The total amount of serum required for the particular patient is first determined and the serum is warmed to body temperature by being placed in a vessel containing hot water The water should not be so hot that the hand cannot be kept in it with comfort If it is too hot it will coagulate the serum and render it useless

Some investigators recommend that epinephrine be added to the serum in order to prevent or minimize an anaphylactic reaction In our opinion this is an unwise procedure because it may mask an anaphylactic reaction by suppressing the symptoms for a while By the time the effect of the epinephrine has worn off and symptoms do appear the vigilance of the attendants may have been relaxed and the anaphylactic reaction may not be detected in time

2 Serum may be administered in several ways

(a) The most convenient method is by syringe We do not advise the administration by this procedure of more than 20 cc at one time since it is difficult if not impossible to give a larger amount slowly enough If more than 20 cc are given one hour should elapse between injections or if a thermal reaction occurs the physician should wait until the temperature has fallen before giving the next injection

(b) Another method of administration is to dilute the serum in 200 to 500 cc of isotonic sodium chloride solution and administer it slowly by gravity This method has the advantage that large amounts of serum

If the patient is definitely allergic to the dander of the animal whose serum is to be used or has responded to previous administration of serum with an anaphylactic reaction serum should not be administered *not even for purposes of testing* unless serum derived from a different animal can be procured In some hypersensitive individuals even a small amount of the diluted serum given intracutaneously can cause a serious or even a fatal reaction

If the patient gives a history of allergy but has never had symptoms on contact with the animal from which the serum is derived testing and serum administration may proceed cautiously

2 Before any testing is done 1 cc of a 1 1000 solution of epinephrine should be placed in a syringe which should be kept along with the bottle of epinephrine at the bedside This should not be removed until the testing and the administration of the serum have been completed and an additional thirty minutes have passed without evidence of a reaction

3 A 1 10 dilution of the serum to be administered is available in most commercial packages of antiserum If not this dilution should be made up One drop is then instilled into the conjunctival sac of one eye This eye is observed for the next twenty to thirty minutes and the other eye used as a control A positive reaction consists of injection of the conjunctival vessels usually accompanied by itching If the test is positive the serum which produced it should not be administered under any circumstances since a positive conjunctival reaction is evidence of a high degree of allergy The symptoms of a positive reaction can be relieved by the instillation of one drop of a 1 1000 solution of epinephrine into the conjunctival sac

4 An intracutaneous test with a 1 10 dilution of the serum should be made on the volar surface of the forearm at the same time as the conjunctival test Only an amount of serum sufficient to make a demonstrable wheal should be injected usually about 0 02 to 0 03 cc The same amount of isotonic sodium chloride solution should be injected into the skin of the opposite forearm as a control A positive skin test will be characterized by enlargement of the wheal usually up to 1 cm or more in diameter together with pseudopods surrounding erythema and usually some degree of itching These appear within five to thirty minutes after the serum is injected The control test should show no enlargement or only a slight amount

If the skin test is markedly positive with many pseudopods and considerable increase in size it is best not to administer more of that animal s serum Antiserum obtained from another animal should be used if it can be obtained and if the patient is not hypersensitive to it If the reaction to the intradermal test is doubtful with increase in size but no definite pseudopods further tests may be made to see if the patient can take larger doses of serum with impunity For this purpose 0 1 cc of a 1 10 dilution should be given subcutaneously If no untoward symptoms

appear within thirty minutes the dose may be doubled and this procedure may be repeated at thirty minute intervals until 1 cc of the undiluted serum is given If there is still no reaction the physician may go on to the next step in the procedure If a constitutional reaction such as the development of hives tightness in the chest a thin sneeze or rhinorrhea develops after any of the injections the attempt to give serum derived from the same animal should be abandoned In our opinion it is impossible to effect rapid desensitization of such a patient in order to make it safe to administer larger doses of serum

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may be given but has also the disadvantages that it is difficult to carry out at home, that the patient s arm must be kept immobile for a long period of time and that someone must be in constant attendance during this period

(c) When the immediate action of serum is not so necessary in instances where the serum is not well purified and concentrated or in patients whose veins are inaccessible the serum may be given intramuscularly The best site for such an injection is the posterior aspect of the thighs although the buttocks or the muscles of the back may be used

3 Whenever a patient receives serum whether there is any reason to suspect allergy or not a physician or a nurse should be in constant attendance during the administration and for thirty minutes afterwards Epinephrine and a syringe should be kept on hand during this time A nurse to whom this duty is assigned should be instructed to administer 0 5 cc of a 1 1000 dilution of epinephrine at the slightest sign of an anaphylactic reaction and at the same time to call a physician

If a patient receives serum for a disease which may require another dose after a long interval it is a common practice to give a small dose of serum five days after the initial injection followed by similar small doses at five day intervals as long as additional doses are likely to be needed These small doses are thought to keep the patient sufficiently desensitized to serum derived from that particular animal so that further doses of serum administered within these five day periods are not likely to be harmful

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4 Sulfonamide Therapy

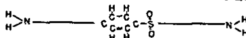
The sulfonamides are the first drugs in all medical history which can be introduced into the body in sufficient concentration to inhibit the growth of bacteria without injuring the tissues of the host. The simplest of them is sulfanilamide. At the present time four additional compounds, more complex derivatives of sulfanilamide, are widely used and many other related substances are available commercially or are in various stages of investigation.

The chemical structures are shown in Figures 5 and 6. The parent substance at the top is sulfanilamide or para-amino-benzene sulfonamide. Some of the derivative compounds are formed by the replacement of a chemical group for one of the hydrogen atoms in the SO_2NH_2 group: the substitution of a pyridine ring forming sulfapyridine, a thiazole group sulfathiazole, or a pyrimidine ring sulfadiazine. Sulfamerazine is the same as sulfadiazine except that it has a methyl group attached to *the carbon atom in the 4 position on the pyrimidine ring.*

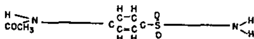
Other less frequently used sulfonamides have chemical formulas as follows: sulfamethazine is similar to sulfadiazine except that it has methyl groups attached to the carbon atoms in the 4 and 6 positions on the pyrimidine ring. In sulfapyrazine a pyrazine ring is substituted for one of the hydrogen atoms in the SO_2NH_2 group. Sulfacetimide is an acetylated derivative of sulfanilamide in which acetylation is carried out at the SO_2NH_2 group. Sulfabenzamine (marfanil) is 4 aminomethyl benzene sulfonamide. It differs from the other sulfonamides in that the amino group is separated from the benzene ring by a methyl group.

Azosulfamide (Neoprontosil) is shown in Figure 5 because it is of historical interest rather than because it is used frequently today. It is an azo dye in which the N in the para position on the benzene ring is joined by a double bond to another nitrogen of a more complex compound. The double bond is broken down in the body to form sulfanilamide as one of its derivatives. It was an azo dye of this kind which was first found by Domagk[4] to be effective in bacterial infections. Not until later was it discovered that sulfanilamide was the active fraction. Succinylsulfathiazole (sulfasuxidine) is sulfathiazole with a succinyl group attached to the nitrogen atom of the para amino radical replacing one hydrogen atom. Phthalylsulfathiazole (sulfathalidine) has a phthalyl group attached to sulfathiazole in the same way that the succinyl group is attached in succinylsulfathiazole. In sulfacarboxythiazole a carboxy

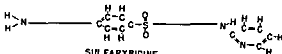
THE
ABSORBABLE SULFONAMIDES



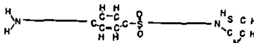
SULFANILAMIDE



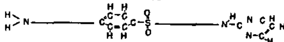
CONJUGATED (ACETYLATED) SULFANILAMIDE



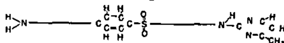
SULFAPYRIDINE



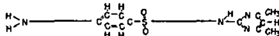
SULFATHIAZOLE



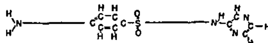
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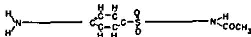
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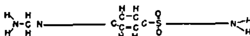
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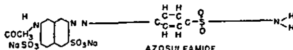
SULFAPYRAZINE



SULFACETIMIDE



SULFABENZAMINE



AZOSULFAMIDE

Fig 5 Chemical structure of the absorbable sulfonamide compounds

group is substituted on the thiazole ring of sulfathiazole In sulfa guanidine a guanidine group is attached to the SO_2 NH_2 group of sulfanilamide

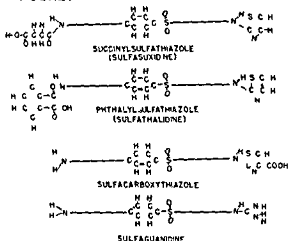


Fig. 6. Chemical structure of the poorly absorbable sulfonamide compounds.

Mode of Action

Within a few hours after one of these compounds is introduced into a culture medium which contains susceptible bacteria, multiplication of the organisms diminishes and under certain circumstances the bacteria die out altogether. Within the tissues of the animal host infected with certain organisms and treated with an effective sulfonamide there is likewise a slowing up of the multiplication of the bacteria as evidenced by their scarcity in contrast to those in the tissues of an infected but untreated animal.

How does this relatively innocuous group of chemical compounds which are dissimilar to all the previously known antiseptics exert such powerful effects upon bacteria? The evidence seems definite that they do not damage the bacteria in the way a protoplasmic poison would, nor do they affect the capsules of the bacteria and thus weaken them. Neither do they act to stimulate the immune mechanism of the host. The sulfonamides apparently act by interfering seriously with the metabolism of the bacteria—just how no one knows for certain. The most widely held theory is that, because of similarity of chemical structure, they compete with para aminobenzoic acid[22] for a place in the enzyme system of the bacteria. When the sulfonamide is in sufficient concentration it displaces para aminobenzoic acid so that the bacteria can no longer obtain nutrition and multiply. Certain substances besides para aminobenzoic acid are known to inhibit the action of the sulfonamides. Especially is this true of peptones and other products of tissue breakdown.[24] It is possible that these substances supply the bacteria with essential foods without

the necessity of the usual enzyme reactions taking place thus allowing them to multiply even though the enzyme system containing para aminobenzoic acid is out of action Whatever the explanation may be this fact has its practical application in explaining why the sulfonamides do not work well in the presence of pus or tissue products

Resistance to Sulfonamides

When a strain of bacteria is cultivated in successively increasing concentrations of a sulfonamide its susceptibility to that sulfonamide diminishes by degrees until it is almost completely unaffected by the drug When experimental animals infected with sublethal doses of an organism and given a sulfonamide are sacrificed and the organism is injected into other animals along with a higher dose of the sulfonamide and this process is repeated until extremely large amounts of the drug are administered the sulfonamide will then lose its power to save the animals from infection by these bacteria When patients have been given a sulfonamide over a period of time without recovery ensuing and comparisons are made between the initial cultures and those obtained after prolonged treatment it has sometimes been found that the sulfonamide has lost its power to cause bacteriostasis of the organisms This phenomenon whether developing in vitro or in vivo is called sulfonamide fastness or sulfonamide resistance

Since these findings have important therapeutic applications certain other observations should be stressed [9] First the tendency to become sulfonamide fast is proportional to the original resistance of the organism to the sulfonamide Second the preponderance of evidence favors the viewpoint that a strain made resistant to one sulfonamide is resistant to all the sulfonamides each drug retaining its original position in the scale of effectiveness Third when sulfonamide fastness has developed in a strain this characteristic remains for some time perhaps indefinitely

Absorption

Certain sulfonamides which are absorbed well from the gastrointestinal tract will be discussed as the absorbable sulfonamides This group comprises sulfanilamide sulfapyridine sulfathiazole sulfadiazine sulfamerazine *and four less frequently used compounds sulfapyrazine* sulfamethazine sulfacetimide and azosulfamide On the other hand sulfaguanidine succinylsulfathiazole phthalylsulfathiazole and sulfacarboxythiazole will be called the poorly absorbable sulfonamides since they are usually absorbed only slightly when administered by mouth

The Absorbable Sulfonamides The rate of absorption for the drugs in the absorbable group is rapid the peak blood level from a single dose being reached in most instances within one to six hours Among the more commonly used compounds absorption is most rapid for sulfanilamide (Table 7) followed by sulfathiazole and then sulfamerazine *sulfa*

pyridine and sulfadiazine. The differences between the drugs are negligible however since they amount to only a few hours at most and since the dosage may be increased or the drug given by another route when extremely rapid effects are desired. Absorption takes place for the most part in the small intestine. It can be accelerated by the simultaneous administration of sodium bicarbonate and will be delayed if the drug is given after a meal.[21]

TABLE 7

RELATIVE RATE OF ABSORPTION AND EXCRETION AND DEGREE OF IONIZATION BINDING AND CONJUGATION OF VARIOUS SULFONAMIDES (COMPILED FROM VARIOUS SOURCES)

Drug	*Relative Rate of Absorption from Intestines*	*Relative Rate of Excretion by Kidneys*	*Relative Degree of Ionization*	*Relative Degree of Binding with Plasma Proteins*	*Relative Degree of Conjugation*
Sulfanilamide	1	1 or 2	4	5	4
Sulfapyridine	4	3	3	4	1
Sulfathiazole	2	2 or 1	2	2	3
Sulfadiazine	4	4	1	3	3
Sulfamerazine	3	5		1	2

Azosulfamide is changed in the gastrointestinal tract to sulfanilamide and appears in the blood in about one third the concentration which would be expected from the same dose of sulfanilamide. Since its actions from that time on correspond to those resulting from similar concentrations of sulfanilamide and since it is seldom used nowadays, it will not be considered separately.

Sulfacetimide when given by mouth is absorbed with the same rapidity as sulfanilamide. Sulfapyrazine is similar to sulfadiazine while sulfamethazine lies between sulfamerazine and sulfadiazine in its absorbability. Only sulfanilamide among the absorbable sulfonamides enters the blood in appreciable amounts when given by rectum.

Sulfanilamide may be given subcutaneously or intravenously. When it is desired to give sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine, sulfamethazine or sulfapyrazine by these routes, the sodium salts are used. Intravenous administration results in high levels immediately. After subcutaneous injection the concentration in the blood rises more slowly. Intraperitoneal administration (usually by sprinkling the crystalline form of the drug in the abdominal cavity) and deposition into surgical wounds often result in high blood levels.

The Poorly Absorbable Sulfonamides. Marshall[7] introduced a new concept in sulfonamide therapy with his discovery that sulfaguanidine, although water soluble and therapeutically active, was not absorbed appreciably from the intestinal tract. Because of the resulting high concentration of the drug in the intestines and low concentration in the

the necessity of the usual enzyme reactions taking place thus allowing them to multiply even though the enzyme system containing para aminobenzoic acid is out of action Whatever the explanation may be this fact has its practical application in explaining why the sulfonamides do not work well in the presence of pus or tissue products

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Ionization The amount of ionization varies according to the drug [11] Sulfanilamide is ionized only slightly whereas sulfathiazole and sulfadiazine are ionized almost completely (Table 7) Since the degree of bacteriostasis achieved is proportional to the amount of ionization it follows that the concentration of sulfanilamide in a particular solution would have to be considerably higher than that of sulfathiazole or sulfadiazine to produce similar therapeutic effects

Binding to Plasma Proteins When a sulfonamide is present in the blood stream a portion of it is bound to the plasma proteins [3] A much greater percentage of sulfamerazine is bound to the proteins than of sulfanilamide with the other sulfonamides falling in between in this respect Since certain membranes are relatively impermeable to the proteins the bound portion of the drug does not penetrate so readily This is especially true of penetration into the cerebrospinal fluid Any sulfonamide compound that may be present in this fluid is for the most part unbound

Binding to plasma proteins is of considerable clinical significance since the unbound portion is apparently inactive therapeutically

Conjugation A certain proportion of a sulfonamide when present in the human body is conjugated by the addition of an acetyl group Para acetyl amino benzene-sulfonamide for instance is derived in this way from sulfanilamide (Fig 5) This conjugation or acetylation probably takes place in the liver The acetylated forms are inactive therapeutically The relative amount of acetylation which occurs in the various sulfonamides is shown in Table 7 Conjugation is more pronounced in sulfapyridine and occurs only slightly in sulfanilamide

Diffusion The absorbable sulfonamides are distributed throughout the various organs and fluids of the body their penetration being influenced by the amount of ionization and the degree of combination with blood proteins Marshall [9] concluded that the amount present in each tissue was proportional to its water content The sulfonamides diffuse into the cerebrospinal fluid and into the body fluids including the pleural fluid the saliva pancreatic juice and bile They pass from the maternal into the fetal circulation and are secreted in the mother s milk although no apparent harm results to the nursing infant from the amounts present in the milk

The ratio between the amount of the drug present in the blood and in the cerebrospinal fluid varies with the sulfonamide administered and also from patient to patient when a particular sulfonamide is employed The concentration of sulfanilamide sulfapyridine or sulfamerazine in this fluid averages about 50 per cent of the concentration in the blood the concentration of sulfathiazole about 30 per cent and of sulfadiazine 75 per cent Thus sulfathiazole diffuses the least freely of all and sulfadiazine the most freely with the other sulfonamides falling in between in this respect

blood and tissues he postulated that it might be of value in the treatment of infections within the intestine Further experience has proved his hypothesis to be correct and subsequently other compounds having similar properties and named succinylsulfathiazole phthalylsulfathiazole and *sulfacarboxythiazole have become available* When sulfaguanidine is given to adults in doses of 0 05 gm per kg of body weight every four hours blood levels of free sulfaguanidine are usually below 3 mg per 100 cc although in an occasional patient the blood concentration will be considerably higher

Because absorption of sulfaguanidine sometimes occurs and because they consider this drug to be ineffectual in the presence of ulcerative lesions of the bowel Poth and his associates[33] have utilized succinylsulfathiazole in its place Succinylsulfathiazole when administered to man in therapeutic doses is found in the blood in concentrations of 0 5 to 1 0 mg per 100 cc of sulfathiazole and from 1 0 to 2 0 mg for the conjugated sulfathiazoles—acetylsulfathiazole and succinylsulfathiazole The greater part of the drug remains in the feces where it apparently has no therapeutic effect until it is converted into sulfathiazole Phthalylsulfathiazole[34] and sulfacarboxythiazole[19] behave similarly to *succinylsulfathiazole*

Excretion

Excretion is for the most part through the kidneys and varies with the drug used being fastest with sulfanilamide and slowest with sulfamerazine Peterson and his associates[32] found that the excretion of sulfadiazine in the urine varied considerably from hour to hour on a constant drug intake and essentially constant fluid intake They were able to accelerate the excretion of sulfadiazine to an appreciable extent by the oral administration of sodium bicarbonate On the other hand a markedly *increased output of urine containing a lower concentration of the* drug was observed when 1500 cc of 5 or 10 per cent glucose in distilled water was injected intravenously The concentration of the drug excreted in the urine is usually between five to thirty times the concentration present in the blood at the same time For sulfaguanidine succinylsulfathiazole *and the other poorly absorbable compounds* the small amounts absorbed into the blood are excreted by the kidneys

Patients with azotemia will excrete sulfonamides more slowly than normal persons so that high blood concentrations sometimes develop Renal excretion also depends upon the reaction of the urine This is *discussed on page 55*

Distribution

After the sulfonamides are absorbed from the intestines or are introduced in any other way several things happen to them Among these are (1) ionization (2) binding to plasma proteins and (3) conjugation

TABLE 8

ADMINISTRATION OF SULFONAMIDES

Absorbable Sulfonamides				*Nonabsorbable Sulfonamides* (*Sulfaguanidine, Succinylsulfathiazole, Phthalylsulfathiazole and Sulfacarboxythiazole*)	
Route	Indication	Method of Administration: Sulfanilamide	Method of Administration: Sulfapyridine, Sulfathiazole, Sulfadiazine or Sulfamerazine	Indication	Method of Administration
Oral	All patients except where contraindicated for special reasons	Tablets of 0.3 gm (5 gr) or 0.5 gm (7½ gr)	Tablets of 0.5 gm (7½ gr)	All conscious patients	Tablets of 0.5 gm (7½ gr)
Intragastric (by nasal tube)	Unconscious or uncooperative patients	Tablets as above crushed in tap water	Tablets as above crushed and suspended in water or as the sodium salt dissolved in water	Unconscious patients	Tablets as above crushed and suspended in tap water
Intravenous	1 Where rapid results are desired In uncooperative postoperative or nauseated patient	1% solution in isotonic NaCl or M/6 lactate solution	Preferably 5 gm in 500 cc M/6 lactate solution May be given in 0.5 to 5% solution in isotonic NaCl or 5% solution in distilled water	Cannot be used If parenteral administration is necessary a soluble sulfonamide should be given	
Subcutaneous	In uncooperative postoperative or nauseated patients	1% solution in isotonic NaCl or M/6 lactate solution	0.5 to 2% solution of sodium salt in isotonic saline solution		
Rectal	In nauseated or unconscious patient	Tablets as above crushed and suspended in tap water	Not absorbed in sufficient quantities	Not used	

METHODS OF ADMINISTRATION AND DOSAGE

The various routes of administration used to obtain systemic effects are shown in Table 8

Oral Administration The sulfonamides should be given by mouth whenever possible In order to develop a high concentration in the blood rapidly the initial dose of the absorbable sulfonamides should be large—usually 4 to 6 gm for a severe infection in an adult followed by 1 gm every four hours day and night Sulfamerazine has approximately the same effectiveness when given in lower doses at less frequent intervals such as 3 gm initially and 1 gm every six hours

In infants and children the usual dose is from 0.06 to 0.12 gm (1 to 2 grains) per pound of body weight for each twenty four hour period divided into six equally spaced doses One half the calculated twenty four hour dose should be given initially

Although it is seldom possible to correlate the height of the blood sulfonamide concentration with the percentage of recoveries in a series of cases there are frequent instances in which raising the concentration in the blood is followed by a prompt fall in temperature and by recovery Consequently arbitrary levels have been set which have been considered as optimal These are for sulfanilamide and sulfamerazine 10 to 15 mg per 100 cc for sulfapyridine sulfadiazine sulfapyrazine and sulfamethazine *8 to 10 mg per 100 cc for sulfathiazole 4 to 6 mg per 100 cc* Usually it suffices however to give the customary doses of the drug and to disregard the blood sulfonamide level as long as the expected clinical results are forthcoming If there is any doubt as to the outcome however the blood level should be raised either by increasing the oral dose or by giving a supplementary intravenous injection

While some authors recommend tapering off the dosage of the sulfonamides gradually it is our practice to continue the full dosage until the drug is stopped

Succinylsulfathiazole is given in doses of 0.25 gm per kg of body weight for each twenty four hour period One half of the twenty four hour dose is administered at the start We have found it more convenient to give 10 gm (150 grains) initially to adults followed by 5 gm (75 grains) every six hours *Children should receive doses in proportion to* their weight Doses of phthalylsulfathiazole and sulfacarboxysulfathiazole are the same Sulfaguanidine is used in doses of 0.1 gm per kg of body weight initially followed by 0.05 gm per kg every four hours

With the use of sulfanilamide sulfadiazine sulfapyrazine and sulfathiazole and the poorly absorbable sulfonamides it is usually not necessary to ascertain the concentration of the drug in the blood because the levels obtained in most cases are sufficient for therapeutic purposes and do not fluctuate widely from day to day when the patient is on the customary doses Determinations are usually necessary when sulfapyridine or sulfamethazine is used because their absorption is irregular and

reasons the patient will not tolerate these amounts) so that the blood concentration will remain at its peak for a long time For prolonged parenteral administration the subcutaneous route should be used the intravenous route being reserved for the initial dose and for instances when it is desired to elevate the existing blood concentration rapidly

Subcutaneous Administration Sulfanilamide is given subcutaneously in a 1 per cent solution and the sodium salts of sulfathiazole sulfadiazine sulfamerazine and the other absorbable sulfonamides in 0 5 to 0 8 per cent solution in M/6 sodium lactate solution or isotonic sodium chloride solution Since the blood concentration reaches its peak in from two to six hours after subcutaneous injections and descends slowly during the next twelve to forty eight hours these injections may be spaced farther apart than the intravenous injections and the resulting blood concentration curves are not so irregular Satisfactory blood concentrations are usually maintained when 1 gm (15 grains) of a sulfonamide is administered every six to eight hours by subcutaneous infusion In children one-sixth of the calculated daily oral dose may be given every six hours It is best however to make frequent determinations of the blood concentration as a guide to therapy

Rectal Administration Sulfanilamide may be given as a 2 per cent solution by rectum in the same doses employed in oral administration The absorption is somewhat slower and the peak levels reached are not so high but otherwise the effects are similar to those obtained by the oral route The other sulfonamides are not absorbed in appreciable amounts when given by this route

Administration by Other Routes The sulfonamides should never be administered intrathecally since this can produce serious injury to the spinal cord

Sulfonamides are also used by sprinkling the powder into open wounds and into the abdominal cavity They have been instilled into the trachea bronchi and sinuses in 1 to 5 per cent solutions Crystalline preparations have been employed for inhalation Sulfonamides have also been incorporated into ointments lozenges and chewing gum and made into cones for dental use

Therapeutic Indications for Sulfonamides

Although the sulfonamides are not employed so universally as they were before the antibiotics became available they are still to be preferred for the treatment of certain conditions As shown in Table 19 (p 100) they are the drugs of first choice in meningococcic meningitis in shigella dysentery in certain urinary infections and in plague They are used in combination with antibiotics in other kinds of bacterial meningitis and in meningococcemia In certain infections where penicillin or streptomycin is the therapeutic agent of choice sulfonamides may be used instead These include pneumococcic gonococcic and hem

when sulfamerazine is employed for any length of time because the slow excretion often causes a high concentration to build up in the blood

Administration by Stomach Tube All the absorbable sulfonamides are absorbed well from the intestinal tract and the nonabsorbable sulfonamides are administered for the purpose of combating the bacteria there Consequently when the patient is unconscious or uncooperative *rather than resort to parenteral therapy it is much better to insert a* tube through the nose into the stomach and inject the crushed sulfonamide tablets suspended in tap water or the sodium salt dissolved in water The doses and intervals are the same as in oral administration

Intravenous Administration Sometimes the patient s illness is so severe that the achievement of the highest concentration of the sulfonamide in the blood in the shortest possible time is imperative For this purpose the intravenous method is especially suitable Sulfanilamide can be used in a 1 per cent solution while sulfapyridine sulfathiazole sulfadiazine and sulfamerazine must be given as the sodium salts in any strength up to a 5 per cent solution The ideal solvent for the latter drugs is one sixth molar sodium lactate solution as shown by Gilligan[15] since the *p*H of the urine is elevated by this solution thus increasing the solubility of the sulfonamides during excretion (see p 55) She has shown that the following formula may be used to approximate the *expected rise in blood concentration following the intravenous administration* of 2 5 gm of sodium sulfadiazine in 0 5 per cent solution in M/6 sodium lactate solution increase in whole blood sulfadiazine concentration (in milligrams per 100 cc) $= \frac{167}{\text{body weight (in kg)}}$ When sodium lactate solution is not available isotonic sodium chloride solution may be used A 5 per cent solution of the drug in distilled water (which makes an isotonic solution) is sometimes employed but is not recommended because the volume of fluid used is low in comparison with the amount of sulfonamide administered The initial intravenous dose of a sulfonamide is the same as that employed when the compound is given by mouth

When the sulfonamides are administered intravenously the concentration in the blood reaches its peak almost immediately remains there as long as the solution is being administered and then falls rapidly to zero over the course of the next few hours A subsequent intravenous injection during the period of fall will raise the concentration in the blood immediately to a new peak its height depending upon the amount injected If repeated intravenous injections are relied upon for continued treatment the curve depicting the blood sulfonamide concentration will resemble a picket fence rather than a straight line Since the latter is to be desired it is the best policy to give intravenous injections of sulfonamides as slowly as possible and in 500 or 1000 cc of fluid (unless for other

reasons the patient will not tolerate these amounts) so that the blood concentration will remain at its peak for a long time For prolonged parenteral administration the subcutaneous route should be used the intravenous route being reserved for the initial dose and for instances when it is desired to elevate the existing blood concentration rapidly

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olytic streptococcic infections and anthrax In other diseases the sulfonamides are employed as adjuncts to the antibiotics

Toxic Reactions

It is an important maxim for the physician to follow that if he does no good at least he should do no harm and that the likelihood of benefit from his treatment should more than balance the harm that might possibly be done Since the sulfonamides are foreign substances in the host it is only to be expected that they will sometimes do injury to the host A good clinician will be familiar with these toxic manifestations will be ever on the watch for the first evidences of them and will know what to do to combat them Table 9 gives the incidence of toxic reactions as we[5 7] have observed them in 2151 patients treated with sulfapyridine sulfathiazole sulfadiazine and sulfamerazine In the subsequent discussion we shall use these figures along with the reactions seen by Long and his associates[5] in 1000 patients treated with sulfanilamide

Table 10 lists the commoner toxic reactions from the standpoint of their importance and the treatment to be used when they occur

Cyanosis

Among the least important toxic effects is the cyanosis which occurs in patients receiving sulfanilamide It was originally attributed to the formation of sulfhemoglobin but is now considered to be due to the presence of methemoglobin and perhaps also of other pigments It should not alarm the physician as it does the patient s relatives and is no reason for discontinuing the treatment If desired a shift may be made to another sulfonamide since only sulfanilamide causes this phenomenon

Acidosis

The carbon dioxide combining power of the blood is lowered in patients receiving sulfanilamide It is a disputed point whether this is due to a primary alkalosis with hyperventilation and a fall in the carbon dioxide content of the serum or whether it is a true acidosis due to *increased sodium excretion a reduced output of ammonia and an elevation* in the pH of the urine The preponderance of evidence seems to favor the latter view It is probably best to give sodium bicarbonate along with each dose of sulfanilamide and to administer this drug parenterally in one sixth molar sodium lactate solution Since it does not occur with the other sulfonamides this condition is of little importance nowadays

Dizziness Headache Mental Confusion

Dizziness and headache occur fairly often as an accompaniment of sulfanilamide therapy seldom with the other sulfonamides Roughton[35] showed that sulfanilamide reduced the capacity for exacting mental work while sulfathiazole and sulfadiazine caused no appreciable changes

TABLE 9

TOXIC REACTIONS FOLLOWING THE ADMINISTRATION OF SULFAPYRIDINE SULFATHIAZOLE SULFADIAZINE AND SULFAMERAZINE

Toxic Reactions	*Sulfapyridine*		*Sulfathiazole*		*Sulfadiazine*		*Sulfamerazine*	
	Pati nts		Patients		Patient		Patients	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Vomiting	10[illegible]	0 1	19	9	11	1 [illegible]	5	1 [illegible]
Renal calculus	8	1 6	9	8	12	1 3	15	3 5
Drug fever dermatitis and/or conjun tivitis	1[illegible]	[illegible] 4	0	6 [illegible]	[illegible]	[illegible] 9	16	3 7
Mental confu ion	1	2 4	[illegible]	1 6	13	1 4	3	0 [illegible]
Leukopenia (with or without granulopen a)	6	1 [illegible]	4	1 2		0 8	4	0 9
Acute hemolytic anemia		1 4	1	0 3	2	0 2	0	0
Leukocyto is	0	0	0	0	[illegible]	0 [illegible]	0	0
(Total patients treated)	(06)		(3[illegible]0)		(900)		(4 8)	
Total patients with toxic react ons	14	9 2	[illegible]	11 5	3	8 1	41	10 0

These symptoms are of no consequence when they occur in severely ill patients but ambulatory patients receiving sulfanilamide should be warned not to drive automobiles or otherwise endanger their own lives or the lives of others while taking the drug Whenever possible they should be given one of the other sulfonamides Mental confusion occurs occasionally during the administration of any of the sulfonamides although it is rarely pronounced Except under special circumstances therapy does not have to be discontinued because of any of the nervous or mental symptoms mentioned for these invariably subside when the sulfonamide is stopped

TABLE 10

TOXIC REACTIONS TO THE SULFONAMIDES GROUPED ACCORDING TO THEIR SEVERITY

	Reaction	*Symptoms and Signs*	*Laboratory Tests*	*Treatment*
Group I Mild reactions	Cyanosis	Blue color of mucous membranes and nail beds and if severe of skin	Spectroscopic examination of blood — used only for investigative work	Continue same sulfonamide or if distressing to the patient change to another sulfonamide
	Acidosis	Usually none—hyperpnea if severe	CO_2 combining power of the blood	
	Dizziness headache mental confusion	Dizziness light headedness headache (usually constant) mental confusion or delirium	None	
	Leukocytosis	None	Leukocyte count	
Group II Moderately severe reactions	Fever	Fever usually reaching height of 102 to 104 F	None	Change to another sulfonamide if treatment is still needed but continue to observe closely
	Dermatitis and/or conjunctivitis	Erythematous morbilliform urticarial nodular or purpuric rash Injection of bulbar conjunctiva and sclera	None	
	Vomiting	Patient may vomit incessantly or only after drug and/or food	None	
	Diarrhea	May be slight or severe and continuous	None	
	Microscopic hematuria	None	Urinalysis	
	Leukopenia	None	Leukocyte count	

TABLE 10—*Continued*

	Reaction	*Symptoms and Signs*	*Laboratory Tests*	*Treatment*
Group III Severe reactions	Hepatitis	Jaundice toxicity	Van den Bergh	Stop sulfonamide immediately force fluids and give sodium bicarbonate by mouth to speed elimination of the drug except when there are renal complications in which event give 5 per cent glucose in distilled water intravenously and force fluid
	Crossed hematuria anuria and/or renal colic	Urine may be blood tinged or grossly bloody Suppression may be partial or complete Pain may be slight or severe	Urinalysis NPN or BUN	
	Peripheral neuritis	Pain or paresthesias along course of any peripheral nerve	None	
	Convulsions	Epileptiform convulsions	Blood sulfonamide concentration	
	Acute hemolytic anemia	Pallor weakness, air hunger	RBC count and hemoglobin Van den Bergh	
	Agranulocytosis	Weakness progression of infection	Leukocyte count and differential	
	Thrombocytopenic purpura	Purpuric areas on skin	Platelet count	

LEUKOCYTOSIS

In an occasional patient receiving sulfonamides the white blood cells may be increased up to 30 000 or even 50 000 per cu mm There is a concomitant increase in band forms and young forms and a few myelocytes may appear This condition may occur independently of other toxic reactions or it may be associated with acute hemolytic anemia The leukocytosis is benign does not call for discontinuance of the drug and disappears promptly when the sulfonamide is stopped

FEVER DERMATITIS AND CONJUCTIVITIS

These three toxic manifestations are grouped together because two of them often and sometimes all three occur together and because they are apparently due to the same underlying mechanism Fever developing as a result of sulfonamide therapy was first described by Hageman[17] It usually occurs from the fifth to the tenth day after the sulfonamides are started but may appear at any time In most instances when it begins on the first or second day of treatment the patient has received the same sulfonamide previously although we have seen drug fever and dermatitis appear on the first day of therapy in patients from whom we could not elicit any history of previous treatment with these drugs Although the temperature graph may assume any form in these cases there is a tendency towards a remittent type of curve rather than a

continuous elevation There is often a steplike ascent of the temperature over the course of the first day or two

Drug fever is sometimes ushered in with a chill If sulfonamide administration is not stopped the fever usually continues unabated although it may stop even under treatment It is often impossible to tell whether a patient is suffering from fever due to a sulfonamide or from an exacerbation of his original disease Leftwich has described an intradermal test using serum obtained from patients while they were receiving a sulfonamide A positive test shows sensitivity to the sulfonamide in question *If this test is confirmed it may be of help in the diagnosis of* doubtful cases

Sulfonamide dermatitis is most frequently erythematous or maculopapular although it may be nodular bullous urticarial or hemorrhagic The erythematous or scarlatiniform type is usually distributed all over the body in such a way that it can be differentiated from the rash of scarlet fever only with great difficulty and sometimes not at all Circumoral pallor and accentuation of the rash in the antecubital areas are not likely to occur however in the drug rash The maculopapular rash closely resembles that of measles and often has the same distribution In many cases especially during sulfanilamide administration a rash may occur only on the face and hands and other portions of the body exposed to sunlight There may be itching with any of the rashes occasionally intense but usually not very severe

Sulfathiazole often causes a nodular rash which is red or dull red in *color and simulates that of erythema nodosum It may consist of only a* few nodules on the anterior aspects of the ankles and legs More commonly there are a number of nodules on the upper and lower extremities and sometimes also the face Occasionally such a rash is distributed all over the body In contrast to other sulfonamide rashes these nodules may be painful We have noticed occasionally a pemphigus like rash following the use of sulfadiazine in which the skin slides off in sheets at the slightest touch All these rashes disappear within a few days after sulfonamides are stopped unless they have reached the stage of an exfoliative dermatitis in which event they may last for months or may be fatal

Injection of the bulbar conjunctiva and of the episclera is found most frequently after the use of sulfathiazole It may occur alone but is more commonly associated with dermatitis Painful joints may also accompany fever and dermatitis

Effect of Repeated Courses of Sulfonamides Lyons[26] showed that fever and rash were more frequent after the second course of sulfathiazole than in patients who had never received the drug previously We[6] found that the incidence of sulfonamide fever and dermatitis depended upon (1) whether the patient had previously developed a similar reaction to an earlier course of sulfonamide therapy and (2) whether the same or a different drug had been administered in the first

course. This is shown in Table 11. When no reaction developed to the first course of sulfonamides, only 3.6 per cent of patients had fever or dermatitis from a second course if a different sulfonamide compound was administered and 11.1 per cent of patients if the same sulfonamide was given. On the other hand, if fever or dermatitis had appeared during the first course, a reaction developed in 16.7 per cent of patients who received a different sulfonamide the second time, while 68.8 per cent of the patients who received the same sulfonamide in the two courses exhibited a reaction. These findings demonstrate that sensitivity to the sulfonamides is usually specific for the individual drug, although in some cases a group sensitivity develops which includes some or all of the sulfonamide drugs. Fever has been observed with the readministration of a sulfonamide many months after the original course.

TABLE 11

FREQUENCY OF DRUG FEVER, DERMATITIS AND/OR CONJUNCTIVITIS DURING FIRST OR SECOND COURSES OF SULFONAMIDES

Reaction to First Course	*Sulfonamides Administered during Second Course*	*Total of Patients*	*Patients Developing Toxic Reactions during Second Course*	
			Number	Per Cent
No	Different drug	169	6	3.6
No	Same drug	141	16	11.1
Yes	Different drug	30	5	16.7
Yes	Same drug	48	33	68.8
	(Control series of persons receiving one course only)	[illegible]	3	[illegible]

It is our opinion that a physician who contemplates prescribing sulfonamides should inquire whether the patient has previously received any of these drugs and, if so, which compound he received and whether he developed any toxic reactions. If fever or dermatitis occurred during a previous course, a different sulfonamide should be administered. If the first course was uneventful, it is still a good practice to employ a different sulfonamide during the succeeding course, provided another drug is available which is as active therapeutically as the first.

Sensitization to sulfonamides is especially likely to occur as a result of the local use of these compounds on the skin or mucous membranes. It is advisable, therefore, to use other substances for topical application in the treatment of local infections whenever possible. The frequency of drug fever and dermatitis can also be diminished if the physician uses a sulfonamide only as long as needed, discontinuing the drug promptly when it has had the desired effect.

Treatment. When fever occurs alone, it is not necessary to stop the sulfonamide, although it is best to change to another drug of equal potency. A rash that has developed will usually disappear if a change is

made to another sulfonamide but if these drugs can be dispensed with altogether it is best to do so In most instances a shift may be made to penicillin or streptomycin Large amounts of sodium bicarbonate by mouth will aid in the elimination of the drug

Gastrointestinal Reactions

How the sulfonamides cause nausea and vomiting has not been determined It is thought that the action is on the central nervous system since it occurs even though the drug is administered parenterally Vomiting is more frequent in white than in Negro patients and in women than in men As shown in Table 9 it is most frequent with sulfapyridine therapy and least frequent with sulfadiazine or sulfamerazine Consequently if this symptom makes its appearance an immediate shift should be made to one of the sulfonamides which seldom cause it If it persists in spite of the drug used and if further therapy is justified the sulfonamide may be given parenterally to ensure absorption Diarrhea occurs only occasionally and may be corrected by changing to another sulfonamide or by parenteral administration

The toxic manifestations in the third group in Table 10 are much more severe and usually call for immediate cessation of all sulfonamide therapy

Hepatic Damage

That the sulfonamides sometimes exert a toxic effect on the liver cells has been definitely demonstrated by Watson[38] and Andersch[1] by means of liver function tests This is substantiated by numerous case reports demonstrating serious and sometimes fatal liver damage following the use of the sulfonamides especially sulfanilamide On the other hand Peterson[30] has shown that sulfadiazine sulfathiazole and sulfapyridine can be used in patients with chronic hepatic damage with little fear of aggravation of the condition In an acute hepatitis associated with bacterial infections he observed improvement in hepatic function paralleling the improvement in the underlying infection He concluded that the presence of damage to the liver should not be considered a contraindication to therapy with sulfathiazole or sulfadiazine

When liver damage has developed as a result of sulfonamide therapy the drug should be stopped immediately fluids should be forced and large doses of sodium bicarbonate given by mouth to accelerate excretion of the sulfonamide A diet high in carbohydrate and protein and low in fat should be given

Renal Complications

Since all the absorbable sulfonamides are excreted for the most part through the kidneys it is important that they should get through the urinary tract without mishap Sulfanilamide does so but the other

soluble sulfonamides often cause trouble These differences are due to variations in solubility of the drugs and their acetyl derivatives Figure 7 shows the solubilities of these substances as they vary in the *p*H ranges

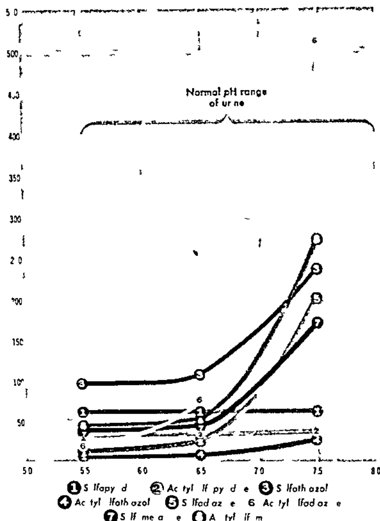


Fig 7 Solubilities of the various sulfonamides and of their N acetyl derivatives at different *p*H levels (Courtesy of Eli Lilly and Company)

usually found in urines In general solubility is less in the acid ranges Among the nonacetylated sulfonamides sulfadiazine is the least soluble at *p*H of 5 5 while acetylsulfathiazole has the lowest solubility of any of the compounds tested at this *p*H By contrast the greatest solubility

among the nonacetylated compounds is that of sulfathiazole at a pH of 7.5 while acetylated sulfadiazine has the greatest solubility of all at this pH. Sulfamerazine and acetylsulfamerazine fall in between the other two drugs with respect to solubility. With sulfapyridine and acetylsulfapyridine alkalinization has no appreciable effect on the solubility.

The sulfonamides are excreted in both free and acetylated forms. As the drug passes through the kidney tubules its concentration may rise from 10 mg. per 100 cc. of blood to 200 or 300 mg. per 100 cc. of urine due to reabsorption of water by the tubules. Sulfanilamide is so soluble that it will remain in solution but if insufficient fluids are left to maintain any of the other sulfonamides in solution the drug precipitates out in the form of crystals. These crystals will adhere to each other and may form a concretion large enough to block a tubule, the pelvis of the kidney or the ureter. If the concretion is smaller it may still cause symptoms of renal colic or microscopic or macroscopic hematuria. If the pH of the urine is high enough or if the output of fluid is large and consequently the water remaining in the tubules after absorption is in sufficient quantity, then the sulfonamide and its acetyl derivative will remain in solution and no concretion will be formed.

Clinical observation bears out these facts. Instances of renal complications—hematuria, pain in the region of the kidneys, oliguria and anuria—have been reported following the use of sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine and even of the poorly absorbed drugs sulfaguanidine and succinylsulfathiazole. In a few cases death has resulted. We[7] have shown that the frequency of renal calculi is greater the higher the maximum blood sulfonamide level achieved. Gilligan[8] and Fox[10] found more sulfonamide crystals in the urine of patients receiving these drugs the lower the pH of the urine. Peterson[3] reported the development of a renal calculus in a patient in spite of a high urinary pH when fluids were considerably restricted.

Prevention. The lesson to be learned from these observations is obvious. In order to prevent sulfonamide calculi the concentration of the drugs in the blood should be kept as low as is consistent with the best therapy, alkalis should be given along with the sulfonamides and fluids should be forced during their administration. An ideal plan for any of the absorbable sulfonamides except sulfanilamide is to give at least 3000 cc. of fluids a day to an adult (and comparable amounts to children), to give 6 gm. of sodium bicarbonate with the initial dose and 3 gm. with each subsequent dose. When it is inadvisable to give large amounts of sodium to a patient because of congestive heart failure or for other reasons, potassium bicarbonate may be given instead in doses of 8 gm. (120 grains) initially and 2 gm. (30 grains) with each subsequent dose of sulfonamide.[23] Flippin,[8] however, states that this adjuvant is not so effective in reducing the incidence of crystalluria as sodium bicarbonate when given in the same doses.

Oral administration is preferable whenever it is possible since calculi are far more frequent when the intravenous and subcutaneous routes are used If it is necessary to give the sulfonamides parenterally each 2 5 gm of the sodium salt should be dissolved in 500 or 550 cc of one-sixth molar sodium lactate solution

Lehr[25] introduced a new principle into sulfonamide therapy by demonstrating that when two or more of these compounds are present simultaneously in the same solution they are soluble to the extent of their separate solubilities In other words an almost completely saturated solution of sulfadiazine can be almost completely saturated with sulfathiazole without precipitation occurring The incidence of intrarenal drug precipitation when Lehr used a mixture of these two drugs was lower than when the same total dose of either drug alone was employed Flippin[9] found that a combination of sulfadiazine and sulfamerazine produced a considerable decrease in the incidence of crystalluria compared with that observed when either compound was administered singly Frisk[14] recommended a combination of 37 per cent sulfathiazole 37 per cent sulfadiazine and 26 per cent sulfamerazine as the most effective mixture We[40] treated 135 patients with a combination of equal parts of sulfadiazine and sulfamerazine The incidence of renal complications was lower than that observed with slightly smaller doses of sulfadiazine or sulfamerazine alone but the differences were not statistically significant

On the other hand the incidence of fever rash and conjunctivitis attributed to the use of the sulfadiazine-sulfamerazine mixture was significantly higher than that due to the use of either drug alone The chances of a patient s developing hypersensitivity phenomena are therefore greater if he is given more than one compound Because these sensitivity reactions may be serious and even fatal and because it is important not to sensitize large numbers of persons to several sulfonamides at one time we believe that combinations of sulfonamides should not be administered as a routine procedure Their use should be reserved for the occasional patient in whom renal complications must be avoided at all costs and for patients who cannot take sodium bicarbonate because the sodium intake must be restricted

Management of Renal Complications Slight irritation from a *sulfonamide concretion may cause microscopic hematuria If this is* observed and it is desired to continue the drug it is safe to do so if the fluid and alkali intake is increased and the urine is observed carefully Graver symptoms are gross hematuria pain in the region of the kidneys or ureters and a diminution or complete suppression of the urine output When these occur during sulfonamide therapy a concretion is the most likely cause Unfortunately the x ray is of no help in diagnosis since these calculi are not radiopaque While microscopic hematuria is an amber light advising only caution any of the graver symptoms flash

the red light of danger and call for immediate cessation of sulfonamide therapy Fluids should be forced and 5 or 10 per cent glucose solution should be given intravenously If anuria is present and is not relieved by these measures the ureter should be catheterized and lavaged with warm sodium bicarbonate solution This is successful in the majority of cases where it is needed but if it is not an operation for removal of the calculus is warranted Decapsulation of the kidney and spinal anesthesia have also been used in such cases with success

COMPLICATIONS INVOLVING THE NERVOUS SYSTEM

Peripheral neuritis occasionally and central neuritis rarely occur after the administration of the sulfonamides Neuritis is most frequent following sulfanilamide therapy although it has been observed after treatment with all the absorbable sulfonamides which have been tested in a sufficiently large number of patients Usually only one peripheral nerve is involved Paresis or paralysis occurs in about one half the cases Neuritis has occurred involving the optic nerve and we have encountered yellow vision in patients receiving sulfathiazole and sulfadiazine Although the neuritides usually disappear soon after discontinuance of sulfonamide therapy patients may fail to recover completely Consequently all patients receiving sulfonamides should be questioned and observed daily for evidences of neuritis and the drug should be stopped on the first sign of their appearance

When the sulfonamides are injected into animals in sufficient amounts to cause high concentrations in the blood signs of irritability of the central nervous system appear including convulsions In the usual concentrations achieved in humans nothing of the sort has been observed but if the concentrations of the sulfonamides reach high levels—above 40 mg per 100 cc for instance—they may occur This phenomenon is probably related to the convulsions which occur in patients when sulfathiazole is placed near the cortex

Since Brenner[7] has shown that sulfathiazole and sulfapyridine both disturb the electrical activity of the cortex while sulfadiazine does so to a lesser extent and sulfanilamide not at all it is important in brain surgery that only sulfanilamide should be applied locally It is likely that higher concentrations of sulfanilamide in the blood stream could be tolerated without the occurrence of convulsions than would be true of the other drugs Although we have never observed fatal convulsions from this source the possibility of death is certainly present

It is important therefore that the concentration of the drug be determined at intervals in patients who have been receiving the drug for long periods of time or in azotemic patients since these latter will excrete the sulfonamides more slowly than normal persons When high concentrations lead to convulsions the drug should be stopped fluids forced and hypertonic glucose solution given intravenously If the concentra

tion of the drug decreases to reasonable therapeutic levels the same or another sulfonamide may be started again in lower doses than before

HEMATOLOGIC COMPLICATIONS

Anemia Slight anemias due to a small amount of gradual hemolysis occur in many patients receiving the sulfonamides[13] Sudden acute hemolytic anemia which was first reported by Harvey[14] is relatively rare especially among the more recently introduced compounds sulfathiazole sulfadiazine and sulfamerazine When it occurs however it may be extremely dangerous with pallor weakness and signs of collapse occurring over a period of a few hours Jaundice vomiting and fever may also appear Autohemagglutinins have been found in some of these cases We feel that determination of the hemoglobin or red blood cells every other day is the only certain way to prevent this reaction from occurring and catching the physician off guard While the severe anemias usually appear during the first few days of therapy they may occur at any time When a mild anemia is observed the sulfonamide may be continued if daily red blood cell counts are done but a sudden decided drop in the hemoglobin concentration calls for immediate cessation of drug therapy and the prompt use of transfusions if necessary

A serious complication of these acute anemias is the plugging of kidney tubules with hemoglobin We have seen anuria and death follow To prevent this the urine should be kept alkaline Another interesting phenomenon which occurs in many patients with acute hemolytic anemia is leukocytosis The white blood cell count may rise as high as 60 000 per cu mm There is a marked shift to the left of the granulocytes at the same time The leukocytes return to normal within a week or two

Leukopenia and Agranulocytosis Like many drugs containing the benzene ring the sulfonamides sometimes cause leukopenia and agranulocytosis The white blood cell count may be depressed only slightly below 4000 per cu mm without any change in the percentages of the component cells or there may be a pronounced drop in the leukocyte count accompanied by diminution or complete absence of the granulocytes Repeated blood counts at least every other day are the only way to detect this phenomenon early It is our policy when the white blood cell count goes below 4000 per cu mm to discontinue the sulfonamide

Although it is admitted that this condition does not always go on to complete agranulocytosis in the face of continued therapy there have been instances in which the count has marched relentlessly downwards even after the sulfonamide was discontinued If the leukocyte count is extremely low penicillin should be given and repeated transfusions liver extract and pentnucleotide may be employed Subsequent doses of the offending sulfonamide have been observed to cause a repetition of this phenomenon It may be well to state parenthetically that if leuko-

penia or agranulocytosis is present *as a result of a severe infection before* the beginning of sulfonamide treatment the sulfonamides are not contraindicated and may be life saving at such a juncture

Purpura Thrombocytopenic purpura is another disorder of the blood caused by sulfonamides which though rare may be quite serious This is shown by Kracke s [1] report of three fatalities among twelve cases reviewed When this complication occurs sulfonamides should be discontinued immediately and measures taken to hasten their excretion

Other Toxic Reactions

French[13] reported pathologic lesions in the heart in patients dying during the administration of sulfonamides This condition is an inter stitial myocarditis containing a number of eosinophilic cells in the exudate Similar lesions were also found[12] in the liver kidney spleen lymph nodes bone marrow and other organs Fibrinoid necrosis of the blood vessels and hemorrhages were also observed Other pathologists have reported similar findings Death has been attributed to these reactions in several instances

Rich[35] considered these pathologic changes to be the result of hyper sensitivity to the sulfonamides Most of the patients had received large doses of the drug for several days and some patients had more than one course of the drug Even though these reactions are relatively infre quent they serve to warn us that it is best not to prolong sulfonamide treatment and that we should beware of second courses of the same drug whenever possible

Incidence of Toxic Reactions in Children

There is some evidence that children do not develop toxic reactions to sulfonamides so frequently as do adults Fink [8] for instance found that in a series of 5000 children who received sulfonamides renal and hematologic complications were rare while only 1 4 per cent of his patients developed fever While these results are encouraging we believe that the same precautions should be followed in the administration of sulfonamides to children as in adults

Relative Toxicity of the Different Sulfonamides

An over all evaluation of the toxic reactions occurring from the use of the sulfonamides should include an opinion as to the relative toxicity of the various compounds Although such judgments must necessarily assume a degree of arbitrariness we are nevertheless hazarding ours because we realize that such a crystallization of present ideas is of great practical value The relative frequencies of the different complications as shown in Table 9 offer an excellent guide

Sulfapyridine The vomiting which occurs in many of the patients receiving this drug is not a serious complication but is an important

one since it often makes proper treatment impossible Furthermore while none of the serious toxic reactions such as renal calculus acute hemolytic anemia or depression of the white blood cell count are extremely frequent they all occur in appreciable numbers These factors together with the observation that there is great irregularity in absorption and thus great difficulty in predicting the blood concentration which will be achieved make sulfapyridine one of the least desirable of the sulfonamide drugs

Sulfathiazole The incidence of drug fever and rash is higher than with any of the other drugs except perhaps sulfanilamide Renal calculi are frequent and focal necroses have been reported in a few cases Except where sulfathiazole is definitely superior therapeutically we prefer to use other less toxic sulfonamides instead

Sulfanilamide The greatest virtue of this compound is that it never causes renal calculi It has however certain disadvantages The cyanosis alarms the patient and the family even if it does no harm Hemolytic anemia and liver damage probably occur more frequently than with any of the other drugs Dermatitis and fever are frequent Consequently we do not use sulfanilamide except occasionally when damage to the kidneys is especially to be feared

Sulfadiazine This drug rates with the best when vomiting fever dermatitis liver damage and hematologic complications are considered Renal calculi are as infrequent following its use as with any of the other drugs except sulfanilamide The extremely high solubility of acetylsulfadiazine in the alkaline ranges of urine gives assurance that renal calculi can be prevented altogether if sufficient alkali and fluids are administered Sulfadiazine diffuses into the cerebrospinal fluid more freely than any other sulfonamide We consider this compound to be the sulfonamide of choice today unless there is a special reason for employing another in a particular patient

Sulfamerazine While this is a newer and less tried drug it has caused few toxic reactions so far We have found it to be of the same order of toxicity as sulfadiazine except that it causes fever and dermatitis slightly more often Renal complications have been more frequent following sulfamerazine therapy but these have been due apparently to the high concentrations of the drug reached in the blood If it is subsequently established that the same therapeutic effects are achieved when *the concentration of sulfamerazine is held at the same level as* that obtained with the usual dose of sulfadiazine then sulfamerazine and sulfadiazine should be interchangeable as the drugs of choice

Second Courses of Sulfonamides

As we have pointed out when discussing the complications of fever and dermatitis a second course of the same drug is more likely to be followed by fever with or without dermatitis than if another sulfonam

penia or agranulocytosis is present as a result of a severe infection before the beginning of sulfonamide treatment the sulfonamides are not contraindicated and may be life saving at such a juncture

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for the presence of red blood cells The fluid intake and output should be measured for each twenty four hour period while the patient is receiv

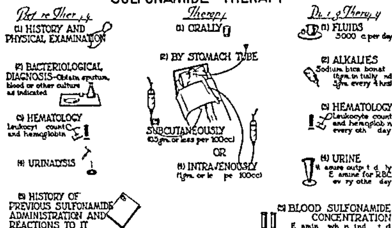


Fig 8 Procedures to be followed in the management of patients treated with sulfonamides

ing sulfonamides and for forty-eight hours afterward If these precautions are taken we believe that a fatal complication of sulfonamide therapy should never occur

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ide is employed for the second course Leukopenia and acute hemolytic anemia sometimes occur when a sulfonamide is given again after it has once caused one of these reactions Accordingly it is clear that if a patient has experienced one of these toxic reactions and needs sulfonamide therapy another sulfonamide should be given for subsequent courses This is true after months or years have intervened If the patient has had a course of a sulfonamide without a toxic reaction it is still best to use another sulfonamide for a second course if it is as effective therapeutically

Deaths from Sulfonamide Toxicity

It is important to stress again that death may occur as a result of several of these toxic reactions exfoliative dermatitis hepatitis renal calculi acute hemolytic anemia agranulocytosis thrombocytopenic purpura and focal necroses in various organs Sutliff[37] estimated that in New York City in 1941 there was one death due to sulfonamide toxicity out of every 685 pneumonia deaths In the treatment of over 4000 patients with various sulfonamides we have observed only one case in which death may have possibly been due to sulfonamide therapy a patient with pneumonia in whom acute hemolytic anemia developed and who died apparently as a result of the two conditions We are even more hopeful of the future of sulfonamide therapy since it appears that the percentage of patients receiving these drugs who develop serious or fatal complications is decreasing year by year There are many factors to account for this (1) an increasing awareness on the part of physicians of the nature and importance of toxic reactions (2) improvement in methods of administration and (3) the discovery of newer sulfonamides which cause fewer toxic reactions than their predecessors

Procedure for the Management of a Patient by Sulfonamide Therapy

Before treatment with sulfonamides is begun as shown in Figure 8 an etiologic diagnosis of the disease should be made if possible and the materials should be obtained for a bacteriologic diagnosis If cultures are needed after sulfonamide therapy has been started the culture medium should contain para aminobenzoic acid for the purpose of inhibiting the action of the sulfonamide thus allowing the growth of any organisms which might be present If possible a complete blood count and urinalysis should be done beforehand After the administration of sulfonamides has been started the patient should be questioned daily for the presence of weakness pains oliguria or hematuria and watched carefully for the appearance of pallor dyspnea jaundice enlargement of the liver or the disappearance of tendon reflexes A leukocyte count and hemoglobin estimate or a red blood cell count should be obtained every other day and the urine examined at the same intervals especially

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In addition to the varieties of penicillin which have been identified and studied there are certain unknown substances which are obtained in the impure preparations Evidence is accumulating to show that some of these substances have an antibacterial action independent of the action of the penicillin itself The clinical significance of these findings cannot be determined until more information has been accumulated

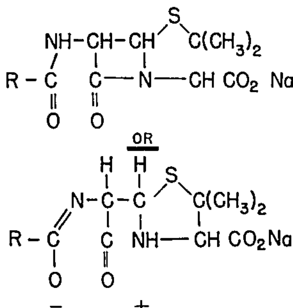


Fig 9 Probable structural formula for penicillin

Nine different salts of penicillin have been prepared (sodium calcium potassium barium magnesium strontium lithium silver and ammonium) Only the sodium potassium and calcium salts have been widely used

PRODUCTION

All the penicillin used commercially up to the present time has been obtained by culturing certain strains of the mold *Penicillium* and then extracting the active substance from the culture medium Although many investigators have attempted to synthesize penicillin these efforts were not successful until duVigneaud[15] recently synthesized small amounts of the drug Commercial production by synthesis at some time in the future now seems likely

POTENCY

Commercial preparations contain mostly benzylpenicillin (penicillin G) plus small amounts of the other penicillins The preparations labeled

5 *Penicillin Therapy*

IN COLLABORATION WITH
HAROLD L. HIRSH

Antibiotics are chemical substances of microbial origin which have the ability either to inhibit or to destroy other micro-organisms including many of the bacteria that cause human and animal diseases. Almost from the dawn of bacteriology attempts were made to develop antibiotic substances which would be effective against human infections. All the substances used for this purpose proved to be too unstable or too toxic for systemic administration until Florey and his associates[10] succeeded in purifying penicillin, a substance discovered by Fleming[20] in cultures of the mold *Penicillium notatum*. Extensive trials have demonstrated that penicillin is strikingly effective against infections caused by a variety of micro-organisms. It is not a panacea, however, and in order to use it wisely the clinician should know certain important facts about it which we shall discuss in this chapter.

Chemistry and Properties

Actually there is not one penicillin but several. The basic formula for them is $C_9H_{11}O_4SN_2R$. The structure is thought to be either of the formulas shown in Figure 9. The five varieties which have been identified are shown in Table 12. It will be seen that the radical "R" in penicillin G

TABLE 12

VARIETIES OF PENICILLIN

Chemical Name	*Former Designation in U S A*	*Former Designation in Great Britain*
Benzylpenicillin	G	II
p-Hydroxybenzylpenicillin	X	III
n-Heptylpenicillin	K	IV
Δ^2-Pentenylpenicillin	F	I
n-Amylpenicillin	Dihydro-F	

is benzyl, in penicillin X p-hydroxybenzyl, and so on. Penicillins G and X are the varieties which have been studied more extensively in clinical work. Investigations made upon penicillin F show that in general it behaves similarly to penicillin G. Comparison of the pharmacological and clinical properties of these varieties will be discussed under the appropriate headings later in this chapter. References to penicillin mean penicillin G unless otherwise indicated.

is used or for twelve months if the penicillin is in the amorphous form The tablets may be kept for eighteen months at room temperature and should be protected against moisture

Penicillin that has been placed in any solution which contains water as an ingredient and that is kept at room temperature begins to lose potency after three days Higher temperatures will inactivate the antibiotic much more quickly so that solutions of penicillin which become *contaminated should not be sterilized by boiling or autoclaving but* rather by passage through Berkefeld Seitz or similar filters

Inactivation of Penicillin Unlike the sulfonamides penicillin is not inactivated by pus by the breakdown products of body tissues by blood serum or para aminobenzoic acid Its action is inhibited by an enzyme called penicillinase which Abraham[1] first prepared from *Escherichia coli* and which has since been isolated from a number of other bacteria *and has been crystallized Penicillinase is of great practical* importance since it can be employed to neutralize the effect of the penicillin present when attempts are being made to culture bacteria from the blood body fluids or wound exudates in patients who are under treatment with penicillin Its effect is similar to that obtained by the use of para aminobenzoic acid in culturing material which contains sulfonamides

Weil[2] have shown that when proper amounts of penicillinase are used the enzyme has an immediate effect and retains its neutralizing power when it is added to a culture medium and kept at incubator temperature We have recommended that 1 unit of penicillinase be added for each cubic centimeter of blood or other body fluid which is to be cultured except urine in which 100 units of penicillinase should be used *for each cubic centimeter of urine*

Cysteine although it can be used to inactivate penicillin in testing *preparations of the antibiotic for sterility has been shown by Hirsh*[3] to be without effect in the presence of protein and therefore unsuitable for use in culturing body fluids

The Action of Penicillin

Action upon Micro-Organisms One of the most remarkable qualities of penicillin is the fact that it is effective against a wide variety of *micro-organisms As a general rule it inhibits the growth of gram* positive bacteria regardless of whether they are aerobic or anaerobic the neisseria group among the gram negative bacteria and in addition certain spirochetes fungi and possibly certain viruses and *Rickettsiae* Figure 10 and Table 13 show the sensitivity of various organisms to *penicillin*

Morphologic changes occur in some bacteria on exposure to penicillin while some organisms undergo lysis

Action on Bacterial Toxins Does penicillin have the same effect upon bacterial toxins that it has upon many bacteria? In general the

penicillin X contain mostly that particular penicillin (p hydroxybenzyl penicillin) together with small amounts of the other penicillins Purified crystalline penicillin is white while the amorphous products vary from light brown to buff depending upon the amount and nature of the impurities present

Penicillin is measured in units The present unit as established by international agreement is the specific penicillin activity contained in 0 6 microgram of a primary standard of crystalline sodium benzylpenicillin (penicillin G or II) In other words 1 mg of the international standard penicillin is equivalent to 1667 units The working standard penicillin established by the United States Food and Drug Administration is of such a potency that 1 mg contains 370 units of penicillin and thus 1 unit of penicillin is equivalent to 2 7 micrograms of the working standard

Methods of Assay All the methods of assay in general use are biological tests which depend upon the inhibition of growth of a microorganism in a culture medium containing the material to be tested compared with the inhibition obtained by a known quantity of a standard preparation The two methods most commonly used in clinical work are the serial dilution and the cup plate methods The latter is based on the principle that when penicillin is allowed to diffuse through an agar plate which has previously been seeded with the test organism a zone of inhibition appears The larger this zone the greater the potency of the penicillin tested

The serial dilution method consists in setting up a series of dilutions of a penicillin solution of unknown strength and a similar series from a standard penicillin solution adding to both a culture of a penicillin sensitive organism and comparing the ability of the two solutions to inhibit growth of the organisms

The serial dilution method which we have found most satisfactory for routine use in the determination of the penicillin content in serum cerebrospinal pleural synovial and other fluids is a modification of the Rammelkamp[16] technique It is given in the Appendix (p 442)

Solubility and Stability

The salts of penicillin are extremely soluble in water whether they are in crystalline form or are present along with impurities as in the amorphous preparations They are stable provided that the *p*H of the medium is between 5 and 7 They are inactivated by acids alkalis primary alcohols and various heavy metals and oxidizing agents

Noncrystalline penicillin may be kept in its solid form for eighteen months without loss of potency if it is stored at 10 C or lower Crystalline preparations may be kept in the solid form at room temperature for three years without deterioration Penicillin in beeswax and oil may be kept at room temperature for eighteen months if crystalline penicillin

Dick tests in human subjects Blair[6] observed that penicillin did not destroy staphylococcal alpha toxin On the other hand Boor and Miller[7, 33] have reported that penicillin protected a large proportion of mice and rabbits against the lethal action of meningococcic and gonococcic endotoxins It seems apparent therefore that penicillin has no effect against exotoxins but may be effective against endotoxins Further investigation is needed to verify the latter point

Mechanism of Action Against susceptible micro-organisms penicillin is bactericidal if used in sufficiently high concentrations When lower concentrations are used the antibiotic has a bacteriostatic effect All the evidence at present favors the viewpoint that only actively growing and multiplying micro-organisms are susceptible to the action of penicillin Exactly how the antibiotic works is unknown It may block an enzyme system needed in or interfere with the utilization of some substance essential for growth or multiplication On the basis of various studies on the inactivation of penicillin with cysteine and related compounds it has been postulated that penicillin combines with the sulfhydryl group and thus prevents the bacteria from utilizing this substance [9] This cannot explain however the specificity of its effects upon a limited range of bacterial types

Hobby[28] working with staphylococci pneumococci and hemolytic streptococci found that the action of penicillin upon these organisms was such that the number of organisms surviving decreased by geometric units as time increased by arithmetic units until 99 per cent of the organisms were killed From this point on the results with different strains varied greatly Sometimes the last 1 per cent were killed rapidly sometimes more slowly and sometimes they survived and multiplied if removed from the penicillin Bigger[5] has called the organisms which survive longer than the others persisters and has evolved the theory that penicillin should be raised intermittently to high concentrations in infected parts of the body He feels that during the periods when the concentrations decrease the persisters will have an opportunity to multiply and will thus be growing actively and will be vulnerable to the peak concentration which will result after the next dose Animal experiments[14] and observations in patients receiving penicillin on the other hand favor the viewpoint that the best therapeutic results are obtained when the concentration of penicillin is maintained at a constant bactericidal level for the duration of the course of treatment In our opinion the latter method is to be followed at least until further evidence is adduced in favor of Bigger s theory

The antibacterial activity of penicillin is increased as the medium becomes more acid and is decreased as it becomes alkaline

The Development of Resistance by Bacteria When strains of bacteria which are naturally susceptible to penicillin are exposed to progressively increasing concentrations of the antibiotic they may adapt

answer is no Neter[34] demonstrated that this antibiotic would not counteract the effects of tetanus toxin in mice and Freoli[17] showed that

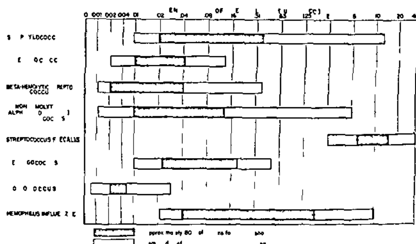


Fig 10 Sensitivity of certain common pathogenic bacteria to penicillin

TABLE 13

SENSITIVITY OF MICRO-ORGANISMS TO PENICILLIN

All or Most Strains Sensitive (Usually below 0 2 units per cc)	Partially Sensitive or Some Strains Sensitive and Others Resistant (Usually between 0 2 and 5 units per cc)	Most or All Strains Resistant (Usually more than 5 units per cc)
Staphylococcus	*Hemophilus influenzae*	*Aerobacter aerogenes*
Pneumococcus	*Hemophilus ducreyi*	*Escherichia coli*
Beta hemolytic streptococcus	*Hemophilus pertussis*	*Eberthella typhosa*
Most strains of alpha and gamma streptococci	*Actinomyces*	*Salmonellae*
Gonococcus	*Corynebacterium diphtheriae*	*Streptococcus faecalis*
Meningococcus	Ornithosis virus	*Shigellae*
Bacillus anthracis	*Clostridium botulinum*	*Brucellae*
Bacillus subtilis		*Klebsiella pneumoniae*
Clostridium perfringens		*Pseudomonas aeruginosa*
Clostridium septicum		*Vibrio cholerae*
Clostridium tetani		*Pasteurella tularensis*
Streptobacillus moniliformis		*Pasteurella pestis*
Erysipelothrix rhusiopathiae		*Proteus vulgaris*
Treponema pallidum		*Monilia*
Treponema pertenue		*Blastomyces*
Leptospira icterohemorrhagicae		*Toxoplasma*
Borrelia novyi		*Plasmodium*
Borrelia vincenti		*Listerellae*
Spirillum minus		Pleuropneumonia like organisms
		Influenza virus
		Lymphogranuloma virus

guinea pigs were not protected against diphtheria toxin by penicillin We[12] have found that penicillin when mixed with diphtheria and scarlet fever toxins has no effect upon the development of positive Schick and

2 The employment of doses of penicillin which are too small to be *completely effective is likely to produce a shift in the bacterial population* in the direction of the more resistant organisms

3 Any factor which prevents access of penicillin to the bacteria will have the same effect as the administration of small doses

Effect of Combinations of Penicillin and Sulfonamides or Serum In view of the universal use of sulfonamides and penicillin it is important to know whether the antibacterial action of the combination is superior to that of penicillin alone Some investigators have stated that the sulfonamides potentiate the action of penicillin while others have felt that they have no effect upon the action of penicillin or may even reduce its antibacterial activity A report by Hobby[25] apparently reconciles these discrepancies She demonstrated that sulfonamides enhance the action of concentrations of penicillin slightly below the effective level while they decrease the effectiveness of bactericidal concentrations of penicillin This latter phenomenon is thought to be due to the fact that sulfonamides slow up the rate of multiplication of bacteria and thus render them less vulnerable to the lethal power of the penicillin Buck[8] has found that doses of antipneumococcic serum and doses of penicillin which were ineffective when administered separately protected mice against pneumococcic infection when the two agents were combined

Clinical experience is in accord with the findings of these investigators If large doses of penicillin are administered there is no evidence that sulfonamides improve the therapeutic results Since the amount of penicillin employed can be increased almost indefinitely because of its low toxicity an unsatisfactory therapeutic response is best combated by increasing the dose of penicillin rather than by giving sulfonamides in addition (A possible exception to this might occur in cases in which the inflammatory process was situated in an area where penicillin would not penetrate well and sulfonamides would such as in the central nervous system and meninges)

On the other hand if the therapeutic response is unsatisfactory in a patient who is receiving sulfonamides alone the increase which can be made in the dose is so small because of the possibility of toxic reactions that the obvious solution is to add penicillin to the therapeutic regimen That this procedure will decrease the case fatality rate in many infections has been demonstrated to the satisfaction of all of us

Combinations of specific antibacterial serums and penicillin have received little clinical trial From the present evidence it would seem that in a patient who was infected with a penicillin sensitive organism but who was receiving doses which were inadequate to effect a cure the best results could be obtained by increasing *the dose of penicillin rather than* by giving serum in addition to the inadequate dose of penicillin In diseases characterized by the formation of exotoxins however such as

themselves to grow in the presence of high concentrations Such resistance of bacteria to penicillin can be induced in animals by treating them with inadequate doses The same phenomenon has been observed at times in human infections Blair[6] reported the development of resistance by staphylococci in osteomyelitis and we have observed it developing in nonhemolytic streptococci and staphylococci in patients with endocarditis

Some investigators believe that resistance to penicillin is acquired as a result of changes which occur in the organism following repeated exposures to penicillin The bulk of the evidence however favors the viewpoint that resistance to penicillin appears as the result of the survival of a few naturally resistant organisms in sublethal concentrations of penicillin These organisms then multiply and predominate According to this explanation penicillin acts as a selecting agent on a population of bacteria allowing only the more resistant ones to live and multiply

Although certain morphological and biological changes occur in strains concomitant with the development of resistance it is important from a clinical standpoint that strains which develop resistance in vivo are still pathogenic Furthermore they usually perhaps invariably retain their resistance for many generations even though they are no longer in contact with penicillin Thus penicillin resistant strains of bacteria may appear in persons treated for therapeutic or prophylactic reasons and theoretically may be transmitted to other persons while they retain the property of being resistant to the antibiotic It has been repeatedly demonstrated that resistance to sulfonamides and to penicillin are independent of each other We[13] have shown that when the resistance of a strain to benzylpenicillin (penicillin G) is increased the resistance of this strain against p-hydroxybenzylpenicillin (penicillin X) is increased at the same time and vice versa

The circumstances affecting the appearance of resistant strains in a patient under treatment with penicillin are not merely a matter for academic discussion This is a practical problem which is inseparable from the question of obtaining the best possible therapeutic results in a given case For this reason it is important that we examine some of the factors which apparently contribute to the development of resistance

1 Assuming that a certain proportion of the organisms in any given bacterial population is relatively resistant to penicillin then the greater the total number of organisms the greater will be the number of resistant organisms present Several factors may contribute to the development and maintenance of a large bacterial population in a given area

(a) the size of the infecting dose
(b) the presence of dead tissue and other debris
(c) anything which obstructs drainage of purulent material
(d) a concurrent infection caused by other bacteria

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Action upon the Host The action and migration of *leukocytes* macrophages or fibroblasts are not affected by penicillin at least not by any concentrations which are likely to be attained in patients Penicillin has no direct influence upon the development of antibodies although it may sometimes abort a disease so swiftly if treatment is early that the bacteria (i e the antigenic stimulus) are quickly eradicated and a maximal antibody response is not elicited Other effects of penicillin upon the host will be discussed under Toxic Reactions (p 83)

Absorption of Penicillin

Absorption after Injection When penicillin is injected intravenously the concentration in the blood serum rises to a peak immediately and then falls rapidly over the course of the next few hours

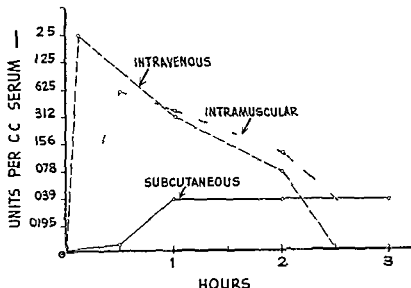


Fig 11 Absorption of single doses of penicillin administered by various routes

(Fig 11) After a single intramuscular injection the serum concentration of the antibiotic rises to its peak (which is lower than the peak which follows the injection of the same amount intravenously) in about thirty minutes and then falls more slowly Absorption from a subcutaneous site is much slower so that the peak of the serum concentration is not reached for about sixty minutes and is relatively low A small amount of the drug can be detected in the serum for several hours afterwards

Penicillin mixed with peanut or sesame oil and beeswax before being injected intramuscularly will be held at the site of injection for some

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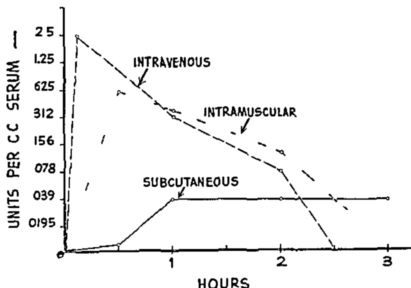


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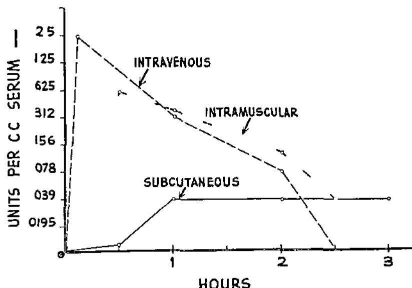


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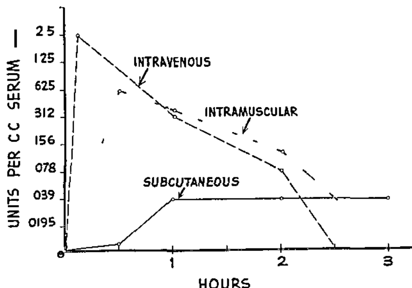


Fig 11 Absorption of single doses of penicillin administered by various routes

(Fig 11) After a single intramuscular injection the serum concentration of the antibiotic rises to its peak (which is lower than the peak which follows the injection *of the same amount intravenously) in about* thirty minutes and then falls more slowly Absorption from a subcutaneous site is much slower so that the peak of the serum concentration is not reached for about sixty minutes and is relatively low A small amount of the drug can be detected in the serum for several hours afterwards

Penicillin mixed with peanut or sesame oil and beeswax before being injected intramuscularly will be held at the site of injection for some

lumen three hours later There is no known method of increasing the proportion of the drug which is absorbed nor of holding the penicillin longer in the small intestine The amount absorbed can be diminished on the other hand by the presence of food which apparently interferes mechanically with absorption Consequently the highest concentrations of penicillin are obtained when it is ingested on an empty stomach or one and one half or more hours after a meal

The penicillin which passes beyond the duodenum is either destroyed in the intestines (presumably by the action of bacteria) or excreted in the stools Although absorption from the jejunum and ileum can take place as readily as from the duodenum a considerable amount of destruction of penicillin takes place in the two distal segments of the small intestine There is little absorption and a large amount of destruction of the antibiotic in the large intestine Absorption from the rectum is undependable and usually negligible in amount

Penicillin X when administered orally is not absorbed so readily and results in lower blood concentrations than similar doses of penicillin C or of commercial penicillin

Absorption from Other Routes When penicillin in doses of 10 000 to 100 000 units is injected into the pleural pericardial or peritoneal and synovial cavities it will be absorbed into the circulation irregularly and in small amounts If doses of 150 000 to 200 000 units are instilled into the pleural cavity therapeutically adequate blood penicillin concentrations are reached and maintained for twelve to twenty four hours Diffusion from the cerebrospinal fluid into the blood probably does not occur except in the presence of inflammation of the meninges and then only in small amounts

Distribution of Penicillin

When penicillin enters the blood about 10 per cent penetrates the red blood cells and a small part of it is bound to plasma proteins With penicillin K however it has been found that a large proportion becomes bound to the plasma proteins This phenomenon accounts in part if not entirely for the rapid diminution of detectable penicillin in the serum after this variety is administered Animal experiments indicate furthermore that the bound portion is not therapeutically active Penicillin passes readily into all the tissues of the body except the nerves bone marrow lens and brain

Diffusion into the Cerebrospinal Fluid The first investigators to study the subject found no evidence of the diffusion of penicillin from the blood into the cerebrospinal fluid while later workers found low concentrations of penicillin in the spinal fluid after systemic administration These differences of opinion were reconciled to a large extent by our observations [14] We found that it was necessary for the concentration of penicillin in the serum to be both relatively high and main

tained for several hours before appreciable amounts of penicillin would appear in the lumbar subarachnoid fluid In further confirmation of this is the work of Schwemlein[39] who has shown that when twenty million or more units of penicillin were administered by continuous intravenous infusion during a twenty four hour period the concentration of penicillin in the spinal fluid at the end of that time was always 0 025 units or higher

Penicillin diffuses readily from the lumbar area to the cerebral portion of the central nervous system after lumbar intrathecal injection of the drug whereas passage is less regular from the cerebral to the lumbar area after ventricular instillation

Diffusion into Other Body Fluids Hepatic bile has been found to contain a concentration of penicillin which exceeds that present in the blood serum at the same time In patients with an obstructed cystic duct however penicillin does not enter the gallbladder[44] Penicillin passes readily into most of the other body fluids the saliva tears edema fluid and breast milk It enters the fetal circulation and amniotic fluid after passage through the placenta

Destruction A small proportion of the penicillin which is injected into the body or absorbed from the gut is destroyed within the body It has been specifically shown that it is not destroyed by the liver There is some debate at present as to whether a large part of penicillin K is destroyed soon after it is absorbed

EXCRETION

Practically all the penicillin which enters the circulation is excreted through the kidney mainly through the tubules Excretion is directly proportional to the blood concentration and unfortunately for therapeutic purposes is very rapid For this reason numerous attempts have been made to find a substance which would block the kidney tubules so as to prevent the egress of penicillin maintain the concentration in the blood for a longer period of time and thus eliminate the need for repeated administration of the antibiotic Such a sequence of events has been observed in renal failure and also when diodrast phenol red hippuran para aminohippuric acid or benzoic acid is administered The last two of these have been used clinically

Para aminohippuric acid[4] is given intravenously first a priming dose of 50 cc in a 6 per cent dilution is warmed to body temperature and injected at the rate of 5 cc per minute followed by a continuous infusion at the rate of about 80 mg per kilogram of body weight per hour These amounts usually result in a para aminohippuric acid plasma concentration of 10 mg per 100 cc The penicillin is given by constant intravenous infusion along with the para aminohippuric acid It is necessary that the renal function be determined beforehand since diminished function might result in high concentrations of the acid in the blood

At the present time another compound caronamide[3] is being investigated to see whether it will block the tubular excretion of penicillin Our investigations thus far have shown that doses of 2 to 4 *gm* every four hours will usually increase the concentration of penicillin in the blood from twofold to eightfold

Penicillin X is excreted more slowly than penicillin G and the total amount of penicillin X recovered is less Penicillin K is excreted more rapidly than penicillin G and the amount recovered in the urine is less than that of either penicillin G or penicillin X

Administration

Administration by Intermittent Injections The intramuscular route is used almost entirely for intermittent injections designed to pro

TABLE 14

MINIMAL SERUM PENICILLIN CONCENTRATION OBTAINABLE FOLLOWING INTRAMUSCULAR INJECTIONS OF DIFFERENT AMOUNTS OF PENICILLIN

(*A*) Penicillin in Aqueous Solution

Amount of Penicillin Injected	*Serum Penicillin Concentration and Time after Injection*		
	2 Hours	3 Hours	4 Hours
(Units)	(Units per cc)	(Units per cc)	(Units per cc)
15 000	0	0	0
20 000	0.02	0	0
25 000	0.04	0	0
30 000	0.08	0.02	0
40 000	0.2	0.04	0
50 000	0.2	0.06	0.02
100 000	0.32	0.16	0.04
200 000	0.63	0.32	0.08
1 000 000	1.25	0.63	0.16
2 000 000	2.5	1.25	0.63

(*B*) Penicillin in Beeswax and Oil

Amount of Penicillin Injected	*Serum Penicillin Concentration and Time after Injection*					
	4 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
(Units)	(Units per cc)	(Units per cc)	(Units per cc)	(Units per cc)	(Units per cc)	(Units per cc)
100 000	0.08	0.01	0	0	0	0
300 000	1.25	0.3	0.2	0.08	0.04	0.0[illegible]
600 000	5.0	0.63	0.63	0.32	0.08	0.04

duce effective serum penicillin concentrations When aqueous solutions are administered injections should be given every two or three hours When penicillin in oil and beeswax is employed the injections may be spaced as far apart as twelve or twenty four hours Table 14 shows the

TABLE 15

DATA ON THE MOST IMPORTANT ROUTES OF ADMINISTRATION OF PENICILLIN

Route	*Advantages*	*Disadvantages*	*Recommended Especially For*
Intermittent intramuscular injections	(1) Simplest parenteral method ( ) Allows for great flexibility of dose	(1) Large number of injections required (2) Penicillin concentrations vary from hour to hour (3) Wasteful of penicillin	General use in hospital when high serum concentrations are not required
Continuous intramuscular infusion	(1) Saving of penicillin (2) Constant penicillin concentrations maintained (3) Easier to administer than continuous intravenous infusion	(1) Sometimes painful (2) Sterile abscesses sometimes form at site (3) Requires constant attendance	In home or hospital when penicillin must be given over a long period of several weeks Under any conditions where it is desirable to save penicillin
Continuous intravenous infusion	(1) Saving of penicillin (2) Constant penicillin concentrations maintained (3) Less painful than continuous intramuscular *infusion* (4) Only method by which highest concentrations can be maintained	(1) Phlebothrombosis sometimes occurs (2) Requires constant attendance (3) Most difficult method to administer	When high serum concentrations are desired and nursing attention is adequate
Injections of penicillin in oil and beeswax	(1) Fewer injections (2) Blood concentrations more constant than with intermittent intramuscular injections of aqueous penicillin solution	(1) Somewhat difficult to administer ( ) Toxic reactions more frequent than with aqueous penicillin	Routine office and home use. Can be used also for routine treatment in hospital
Oral	(1) Simplest method ( ) No attendants required	(1) Blood concentrations irregular (2) Minimal concentrations maintained are low, therefore suitable for certain infections only	Office, home or hospital use in infections which respond well to penicillin

doses needed at the various intervals to produce certain desired minimal blood concentrations

Administration by Continuous Infusion When high blood concentrations of penicillin are needed the most satisfactory method of administration is by continuous intramuscular or intravenous infusion (Fig 12) In intramuscular infusions the amount of penicillin desired for each twelve hour period is calculated and that amount is dissolved in 500 or 1000 cc of isotonic sodium chloride solution [3] If it is desirable to limit the quantity of sodium administered 5 per cent dextrose solution may be used instead The solution is placed in a flask and connected with a Murphy drip apparatus to which a 2 inch 18 or 20 gauge needle is attached The needle is inserted into the lateral aspect of the thigh or into the gluteal muscles the solution flows at a constant rate over

Fig 12 Absorption of penicillin during a twenty four hour period when it is administered by various methods

the course of twelve hours When 1000 cc of solution are used for a twelve hour period the proper rate of flow is usually thirty to forty drops a minute If the patient complains of pain at the site of injection 25 cc of 1 per cent procaine may be added to each 500 or 1000 cc of solution

For continuous intravenous infusions the Murphy drip is used likewise and the solution is made up as for the continuous intramuscular infusion A 20 gauge needle is inserted into a vein preferably one well below the elbow so that the patient will have more freedom of movement The needle should be anchored firmly in place with adhesive Veins in the legs can be used if desired

The site of the injection should be inspected at frequent intervals for evidences of irritation As soon as these are observed the needle should be removed immediately to another site In this way thrombophlebitis

can be prevented almost entirely Another method of preventing it is to add 1 unit of heparin to each cubic centimeter of the solution

When penicillin is administered by either the continuous intramuscular or the continuous intravenous method the serum penicillin concentration rises rapidly to a plateau and this level is maintained as long as the infusion is being given (Fig 12) Although there is considerable variation from patient to patient and in the same patient from time to time a rough estimate can be made of the serum penicillin concentration on the basis of the penicillin dosage For every 100 000 units given over a twenty four hour period the serum concentration will rise approximately 0 1 unit per cc

For moderately severe infections twenty four hour doses of 500 000 to one million units will often be sufficient For more severely ill patients or for infections caused by relatively resistant organisms doses up to forty million units or more have been employed For these larger doses the continuous intravenous infusion is preferable

Continuous infusions may also be administered into the bone marrow The most commonly used site is the sternum Recourse to this route may be necessary in cases where the veins are thrombosed or inaccessible

Oral Administration The serum penicillin concentrations obtained after administration of the drug by mouth are so variable that one cannot predict with certainty the concentration which can be obtained after a particular dose Penicillin has been used successfully in several diseases by administering at three hour intervals doses five times as great as would be employed intramuscularly for the same conditions The drug is administered most conveniently in the form of tablets in which the penicillin is usually combined with an alkaline buffer but if tablets are not available penicillin powder may be diluted with water and given in this way

More constant and predictable blood concentrations are obtained when the doses are spaced so as to fall at least one half hour before and one and one half hours or more after meals

Intrathecal Administration In all the diseases of the nervous system which are benefited by penicillin with the exception of neurosyphilis penicillin has been administered intrathecally The lumbar subarachnoid space is most commonly used since injections there are more convenient and less dangerous although the injections may also be made into the lateral ventricles or intracisternally Doses of 10 000 to 20 000 units dissolved in 2 to 10 cc of isotonic salt solution should be administered by slow injection or by gravity after a slightly greater volume of spinal fluid has first been removed Larger doses should not be used since symptoms of irritation and shock have been observed as a result of the intraventricular injection of 15 000 to 50 000 units of penicillin and permanent cerebral and cranial nerve damage arachnoid

itis transverse myelopathy and peripheral neuritis have followed intra thecal injections of similar doses Similar injurious effects which have occasionally resulted from injections of 10 000 units in the lumbar sub-arachnoid space are probably due to the building up of high spinal fluid *concentrations of penicillin as the cumulative result of daily injections* for ten or more days For this reason it is good practice to determine the concentration in the spinal fluid at least every second or third day when intrathecal therapy is being continued over a long period Intra thecal injections of penicillin which are not sufficiently diluted or which are given too rapidly may also produce damage to the spinal cord

Injections into the Pleural, Peritoneal and Pericardial Spaces Although penicillin administered systemically is absorbed into the serous cavities it cannot be depended upon to reach and remain at a desired concentration in a given case Infections of these serous membranes must therefore be treated by the local injection of penicillin Doses of 30 000 to 200 000 units of penicillin in a dilution of 1000 to 10 000 units per cc of isotonic salt solution should be injected daily or on alternate days When underlying pulmonary disease is present penicillin should also *be administered systemically*

Intra-Articular Injections Most bacterial infections of the joints should be treated by the intra articular injection of penicillin Doses of 50 000 units each day or 100 000 units on alternate days in dilutions of 1000 to 20 000 units per cc should be injected As much synovial fluid as can be obtained is first removed An exception to this is gonococcic arthritis which often responds to systemic therapy alone

Inhalation Penicillin administered by inhalation is an effective form of therapy for certain diseases of the respiratory system Doses of 20 000 to 200 000 units of penicillin dissolved in 1 to 1 5 cc of isotonic salt are administered by having the patient inhale the nebulized solu tion delivered through a special apparatus The reader is referred to the work of Barach[2] who has pioneered in this field for further par ticulars

Other Methods of Administration Penicillin can be applied locally as a spray by means of saturated dressings or through tubes into deeper wounds Concentrations of 250 to 5000 units per cc are used Irrigations with penicillin solution should not be employed since this method does not keep the antibiotic in contact with the wound for a *long enough period Penicillin is also applied locally as a powder* oint ment or cream Troches for dissolving in the mouth are available com mercially although their value in the treatment of infections of the mouth has not been definitely established at the present time

Serum Concentrations Obtained in Children While it is quite likely that *identical doses of penicillin will produce higher serum con* centrations in children than in adults, the differences are certainly not proportional to the difference in body weight Until more studies have

been done in this connection it is best to give most children the same doses as are recommended for adults In infants a dose of one half the size of an adult dose should be sufficient

Toxic Reactions

Although penicillin is the least toxic of all known antibacterial agents nevertheless its administration is sometimes accompanied by untoward reactions which are usually merely uncomfortable occasionally serious and rarely fatal In the early days of penicillin therapy many reactions were observed which were due to impurities which had not been removed Among these were chills fever headache flushing of the face and skin rashes As the preparations of penicillin have become progressively purer and especially since crystalline preparations have been available it has been possible to distinguish those reactions from the ones due to penicillin itself

Irritant Reactions

Reactions to Injection When injected intramuscularly pure preparations of penicillin seldom produce any more discomfort than a slight burning or stinging sensation which passes away after a few minutes If this bothers the patient unduly 1 cc of 1 per cent procaine solution may be added to the penicillin solution before injection The less pure preparations sometimes produce more pain and discomfort Subcutaneous injections are generally more painful than those given into the muscles

Pain at the site of continuous intramuscular infusions may occur if the needle is inserted in a place where the amount of fluid which can be inserted is limited for instance between the skin and a fascial plane Aseptic necrosis has been observed in rare instances as a result of continuous intramuscular infusions Continuous intravenous infusions sometimes result in thrombophlebitis at the site of the injection Thrombophlebitis is appearing less frequently as the preparations of penicillin are becoming purer The incidence can be decreased still further by adding heparin in quantities of 1 unit per cc of fluid This reduces slightly the speed of coagulation at the site of injection without affecting the coagulation time generally When thrombophlebitis does occur it subsides within a short time after the needle has been moved to another vein

Oral Administration Oral administration is usually not attended by symptoms of gastrointestinal irritation We have observed nausea rarely mild diarrhea twice and vomiting only once among more than 300 patients who received the antibiotic by this route These symptoms were more likely due to the mechanical irritation caused by several tablets than to the action of the antibiotic itself

Serous and Synovial Cavities Penicillin is somewhat irritating

when it is injected into serous cavities Some of our patients have complained of pain of the pleuritic type at the time when the drug was being injected intrapleurally and some have developed lymphocytosis of the pleural fluid after the injections When penicillin was injected into normal joints we noted slight redness swelling tenderness and pain on motion of the joint followed by lymphocytosis of the synovial fluid These phenomena invariably disappeared entirely within forty eight to seventy two hours

Central Nervous System Penicillin has shown the greatest irritant effect in the central nervous system Damage to the spinal cord from doses of penicillin which are too large or too concentrated or from the building up of high concentrations of penicillin in the cerebrospinal fluid has already been discussed (p 81) Large doses of penicillin administered intraventricularly or intracisternally will cause cyanosis symptoms of shock convulsions and death[18, 43] These reactions cannot be attributed solely to the impurities in commercial penicillin since they have also followed the employment of the crystalline product The administration of penicillin directly into the cerebrospinal fluid is followed by an increase in the number of lymphocytes in the fluid This phenomenon has no particular significance except that it is an evidence of irritation and may confuse the diagnosis or prognosis unless it is borne in mind

Uterus Although it has been stated that penicillin administered systemically has a toxic effect upon the uterus which may result in abortion careful studies of the cases of a large number of pregnant women treated with penicillin have failed to substantiate this contention[41] We do not believe there is any reason for withholding penicillin treatment from a woman because she is pregnant

Reactions Apparently Due to Hypersensitivity

Local Reactions Contact by penicillin solution spray or ointment with the skin may produce a local reaction which is apparently due to hypersensitivity since the antibiotic is not a primary irritant when applied to the skin The resulting dermatitis may be erythematous vesicular bullous or exfoliating and will be accompanied by varying degrees of edema weeping and itching Contact with the eyes may produce conjunctivitis blepharitis and scleritis Even the slight amount of powder which is carried to the eyes of a person opening an ampule may be sufficient to produce a conjunctivitis Fortunately this condition is encountered infrequently

When penicillin is applied to the membranes of the mouth nose or throat by means of mouth washes gargles sprays troches or tablets the membranes may become swollen red and vesicular and may exfoliate Subsequent administration of penicillin locally or systemically is likely to cause another attack in the area previously involved

General Reactions The clinical manifestations of these (Fig 13) are

1 Skin rashes morbilliform erythematous purpuric vesicular or exfoliative erythema multiforme and erythema nodosum
2 Angioneurotic edema
3 Malaise general aching and fever
4 Generalized lymphadenopathy
5 Pain and swelling of the joints
6 Dyspnea pulmonary edema
7 Nausea vomiting abdominal cramps
8 Syncope and shock
9 Peripheral neuritis

It is evident that many of these manifestations are characteristic of serum sickness (skin rashes arthralgia lymphadenopathy) while others are typical features of immediate serum reactions or accelerated serum

Fig 13 Procedures to be followed in therapy with penicillin

sickness (angioneurotic edema vomiting abdominal cramps dyspnea and syncope) Others such as erythema nodosum and exfoliative dermatitis are frequently seen in patients who are hypersensitive to certain drugs

Peripheral neuritis which is included in the list merits special discussion Kolb [8] has reported seven cases which had their onset from ten to twenty-one days after the initial injection of penicillin The common peroneal nerve was affected in three cases the sciatic in one and the lateral femoral cutaneous in another the remaining two patients had involvement of nerves which arose from the brachial plexus The motor disability was much more pronounced than the sensory changes in each

when it is injected into serous cavities. Some of our patients have complained of pain of the pleuritic type at the time when the drug was being injected intrapleurally, and some have developed lymphocytosis of the pleural fluid after the injections. When penicillin was injected into normal joints we noted slight redness, swelling, tenderness and pain on motion of the joint, followed by lymphocytosis of the synovial fluid. These phenomena invariably disappeared entirely within forty eight to seventy two hours.

Central Nervous System. Penicillin has shown the greatest irritant effect in the central nervous system. Damage to the spinal cord from doses of penicillin which are too large or too concentrated, or from the building up of high concentrations of penicillin in the cerebrospinal fluid has already been discussed (p. 81). Large doses of penicillin administered intraventricularly or intracisternally will cause cyanosis, symptoms of shock, convulsions and death.[18, 43] These reactions cannot be attributed solely to the impurities in commercial penicillin, since they have also followed the employment of the crystalline product. The administration of penicillin directly into the cerebrospinal fluid is followed by an increase in the number of lymphocytes in the fluid. This phenomenon has no particular significance except that it is an evidence of irritation and may confuse the diagnosis or prognosis unless it is borne in mind.

Uterus. Although it has been stated that penicillin administered systemically has a toxic effect upon the uterus which may result in abortion, careful studies of the cases of a large number of pregnant women treated with penicillin have failed to substantiate this contention.[41] We do not believe there is any reason for withholding penicillin treatment from a woman because she is pregnant.

Reactions Apparently Due to Hypersensitivity

Local Reactions. Contact by penicillin solution, spray or ointment with the skin may produce a local reaction which is apparently due to hypersensitivity, since the antibiotic is not a primary irritant when applied to the skin. The resulting dermatitis may be erythematous, vesicular, bullous or exfoliating and will be accompanied by varying degrees of edema, weeping and itching. Contact with the eyes may produce conjunctivitis, blepharitis and scleritis. Even the slight amount of powder which is carried to the eyes of a person opening an ampule may be sufficient to produce a conjunctivitis. Fortunately this condition is encountered infrequently.

When penicillin is applied to the membranes of the mouth, nose or throat by means of mouth washes, gargles, sprays, troches or tablets the membranes may become swollen, red and vesicular and may exfoliate. Subsequent administration of penicillin locally or systemically is likely to cause another attack in the area previously involved.

penicillin administration It has been suggested that these may be due to sensitization to the antibiotic *in utero* or as a result of previous contact with the mold *Penicillium*

Sensitization of the skin and mucous membranes by direct contact is the most frequent form of sensitization Kolodny[9] observed that immediate reactions developed in 25 per cent of dermatologic patients and in 6 per cent of nondermatologic patients while delayed reactions were present in 8 per cent of the former and 10 per cent of the latter

Tests for Hypersensitivity The fact that hypersensitivity to penicillin does exist is strengthened by the demonstration in some patients who have shown reactions of positive intracutaneous patch and passive transfer tests and rarely of positive precipitin reactions also The first three of these have been elicited with crystalline as well as commercial penicillin The interpretation of these reactions is complicated however by the fact that positive tests do not occur in all individuals who manifest the symptoms characteristic of hypersensitivity to penicillin while on the other hand a number of normal persons react positively Rostenberg[28] for instance observed positive skin tests of the tuberculin type in 5 per cent of 114 persons who had had no prior contact with penicillin

Treatment

None of the tests which have been utilized up to the present time can be depended upon to detect persons who are hypersensitive to penicillin This must be accomplished therefore by inquiring for the occurrence of reactions to a previous course of penicillin and by observing carefully all patients who are receiving this antibiotic Fortunately the reactions indicative of hypersensitivity usually disappear within a few days if *penicillin therapy is discontinued and even in some instances while penicillin* is still being administered Exfoliative dermatitis however may progress even though penicillin is no longer being given and at least one death has occurred in this way Another death attributed to penicillin occurred in a patient with a scarlatiniform and urticarial rash Other patients have exhibited serious and sometimes alarming reactions

Penicillin therapy should accordingly be discontinued in all patients with a vesicular bullous or exfoliative rash and in instances where the rash is accompanied by a considerable amount of edema or a marked degree of urticaria Angioneurotic edema involving the air passages dyspnea pulmonary edema syncope or incipient shock are also indications for cessation of penicillin treatment The drug should also be discontinued if peripheral neuritis appears unless the disease from which the patient is suffering is likely to terminate in death if more penicillin is not given As far as can be determined penicillin need not be stopped if the following reactions are present fever and malaise nausea and vomiting lymphadenopathy or urticarial erythematous or maculopapular rashes provided they are not extensive If penicillin therapy is

case Muscular atrophy appeared in two patients with lesions of the brachial plexus Complete recovery occurred within four months in five of the patients while the other two had improved considerably when the report was made

Because of the time interval which elapsed before the appearance of the neuritis and because the clinical features of this condition resembled the neuritis which often occurs as a part of serum sickness we have included this syndrome among the reactions of hypersensitivity rather than attributed it to the direct action of penicillin upon the nerves It is important to note however that most investigators have encountered peripheral neuritis rarely or not at all It is possible that many of Kolb s cases may have been caused by something other than the penicillin

Dermatophytide Reactions Generalized eruptions following the administration of penicillin have appeared in patients with chronic mycotic infections of the feet or hands These rashes are similar to the dermatophytides frequently observed in patients with dermatophytoses

Herxheimer Reactions Patients with syphilis especially those in the primary or secondary stages often exhibit Herxheimer reactions when penicillin is administered These are characterized by fever chills edema and pain at the site of the syphilitic lesion nausea malaise headache or joint pains or a combination of these symptoms[21] In most cases they appear from two to eight hours after the beginning of penicillin treatment and last for twelve to twenty four hours They are thought to be a reaction to the products of destruction of the spirochetes Olansky[33] *has shown that they cannot be prevented by giving small doses of penicillin* at the start of treatment as has been advocated by some workers

Other Reactions Penicillin accelerates the coagulation of animal and human blood One case of agranulocytosis has been reported as being probably due to penicillin Nicotinic acid deficiency has been observed in a patient who was given penicillin orally Although there have been occasional cases in which azotemia developed while patients were receiving penicillin the scarcity of such occurrences makes it unlikely that penicillin itself was responsible Some investigators have claimed that penicillin potentiates the anticoagulant action of heparin while several other workers have been unable to confirm this There seems to be no reason therefore why heparin and penicillin cannot be given concomitantly

Relation to Previous Penicillin Therapy Patients receiving penicillin may become sensitized to it in the same way that people become sensitized to serum or drugs with the result that any of the reactions listed on page 85 may take place These reactions are usually of the delayed type since they occur in most instances from five to twenty five days after the start of penicillin therapy On the other hand they may appear immediately after the administration of the first dose of penicillin if a course of the antibiotic has recently been given Sometimes immediate reactions occur when there has been no history of previous

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continued under these circumstances the patient should be observed carefully and at frequent intervals

The treatment of the reactions once they have developed is similar to that employed for reactions following the administration of serum Urticaria will be relieved for short periods by the use of 0 3 to 0 6 cc of a 1 1000 solution of epinephrine (Larger doses are seldom required and only serve to make the patient uncomfortable from the side effects) Injections of 0 5 to 1 0 cc of a 1 500 solution of epinephrine in oil may be effective for as long as eight to twelve hours Benadryl or pyribenzamine in doses of 50 mg every two to three hours for adults and in proportionate amounts for children may be used instead and will often be effective We have not found ephedrine effective except in very mild urticaria

The itching may be alleviated by local application of calamine lotion containing 1 per cent phenol and by baths in water containing starch or sodium bicarbonate Arthralgia is often relieved by aspirin This drug may also keep down the fever somewhat and relieve the headache

In the event of an immediate reaction the administration of penicillin should be promptly discontinued Epinephrine hydrochloride solution 1 1000 should be administered intramuscularly in doses of 0 5 to 1 0 cc and the site massaged vigorously in order to speed entry of the drug into the circulation If the patient s condition requires more urgent action 0 3 cc of this solution should be given slowly into a vein If the veins are collapsed and death appears imminent the epinephrine may be given directly into the heart Injections of epinephrine should be repeated at intervals as required until the patient is completely free from danger or relapse This means that he must not be unattended for a moment during this time The xanthine diuretics and oxygen under positive pressure may be used to combat pulmonary edema Shock and syncope should be treated by the usual methods

Subsequent Penicillin Therapy Patients who have reactions due to sensitization of the skin or mucous membranes to penicillin should be given penicillin a second time whether it be locally or systemically only if the antibiotic is urgently needed and then cautiously and in small doses at first

Under what circumstances penicillin can be readministered with impunity to a person who has experienced a reaction of the serum sickness type is not settled at the present time Even though penicillin does not seem to be so dangerous in this respect as serum it would be well to withhold it unless the patient is suffering from a severe illness and then to give it only with the utmost caution

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6 Streptomycin Therapy

IN COLLABORATION WITH
HAROLD L. HIRSH

After the discovery of penicillin many attempts were made to find another antibiotic which would inhibit the growth of organisms that are unaffected by penicillin especially the gram negative bacteria It was necessary that this antibiotic should not be inactivated by body fluids and that it would be relatively nontoxic to humans The substance which has been most successful in fulfilling these criteria is streptomycin obtained from cultures of several strains of *Actinomyces griseus* Subsequent studies in animals and in human patients have demonstrated the effectiveness of this substance in many diseases

Chemistry and Properties

The chemistry of streptomycin is not completely known at the present time It has been shown to be an organic base with the probable formula of $C_{21}H_{37-39}N_7O_{12}$ It is soluble in water and insoluble in ether acetone and chloroform It is available as a white powder in the form of streptomycin hydrochloride sulfate phosphate or the double salt of calcium chloride

Production

The crude antibiotic is obtained from the culture of *Actinomyces griseus* by adsorption upon charcoal After elution it is purified concentrated and crystallized and converted into one of the soluble salts

Potency

Formerly streptomycin was measured in terms of units an S unit being that amount of material which when present in 1 ml of nutrient medium will just inhibit the growth of a given strain of *E coli* Other units were designated an L unit which was 1000 times an S unit and a G unit which was approximately 1 000 000 times an S unit or 1000 times an L unit These units have no relation to units of penicillin Since crystalline streptomycin has become available the standard has been based upon the weight of the dry material as follows

Weight of Streptomycin Base	*Approximate Equivalent in Units*
1 microgram	1 S unit
1 milligram	1 L unit (1000 S units)
1 gram	1 G unit (1000 L units)

26 Hobby G L Meyer K and Chaffee E Observations on the Mechanism of Action of Penicillin Proc Soc Exper Biol & Med 50 281 1942
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28 Kolb L. C and Gray S J Peripheral Neuritis as a Complication of Penicillin Therapy J A M A 132 323 1946
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Mechanism of Action The mechanism of action of streptomycin cannot be determined at the present time Bondi[2] has made the suggestion that its antibacterial action may be due to its ability to block an oxidative enzyme substance which is essential to the growth of aerobes If the enzyme blocked by streptomycin were one which is not necessary for the metabolic processes of anaerobes this would explain the failure of streptomycin to affect anaerobes in general

The Development of Resistance in Bacteria One striking characteristic of streptomycin is the ease with which bacteria which were originally susceptible can be adapted so that they will become resistant to high concentrations of the antibiotic Resistance to streptomycin is acquired with much greater facility than resistance to penicillin both

TABLE 16

SUSCEPTIBILITY OF VARIOUS MICRO-ORGANISMS TO STREPTOMYCIN

Very Susceptible	*Moderately Susceptible*	*Slightly or Nonsusceptible*
Generally less than 1 microgram per cc.	Generally between 1 and 20 micrograms per cc	Generally over 20 micrograms per cc
Aerobacter aerogenes *Bacillus anthracis* *Mycobacterium tuberculosis* *Pasteurella pestis* *Pasteurella tularensis*	*Brucella abortus melitensis and suis* *Corynebacterium diphtheriae* *Diplococcus pneumoniae* *Eberthella typhosa* *Escherichia coli* *Hemophilus influenzae* *Hemophilus pertussis* *Klebsiella pneumoniae* *Neisseria gonorrhoeae* *Neisseria intracellularis* *Proteus vulgaris* *Pseudomonas aeruginosa* *Salmonellae* *Shigella paradysenteriae* *Staphylococcus aureus* *Streptococcus hemolyticus* *Streptococcus salivarius* *Streptococcus viridans*	*Clostridium septicum* *Clostridium tetani* *Clostridium welchii* *Staphylococcus aureus* (some strains) *Streptococcus faecalis* *Pseudomonas aeruginosa* (some strains)

in vitro and in patients under treatment It is independent of and not related to resistance to penicillin or the sulfonamides

The origin of resistant organisms is not known They may be derived from originally sensitive strains the growth requirements of which are changed after exposure to streptomycin or they may have been present in small numbers in the bacterial population before the first contact with the antibiotic In the latter event they would have become the predominant organisms by surviving the destruction of the more susceptible ones The latter theory best explains the facts which are known at the present time

The acquisition of resistance to streptomycin is of tremendous clin

Methods of Assay Streptomycin can be assayed only by biological methods which depend upon the inhibition of the growth of a susceptible micro-organism in a culture medium containing the material to be tested compared with the inhibition obtained by a known quantity of a stand ard preparation Assays are frequently done by determining the area of diffusion through an agar plate seeded with micro-organisms The streptomycin may be placed in glass cups or on filter paper discs We have used a serial dilution method devised by the Food and Drug Adminis tration which is similar to that used for penicillin except that the test organism is a strain of *Bacillus circulans* The technique is given on page 112

Stability

The salts of streptomycin in powder form can be stored for eighteen months in the refrigerator without appreciable loss of potency Dilute sterile solutions are best stored in the refrigerator although these have been shown to maintain their potency for at least sixty days at room temperature When the antibiotic is heated at 100° C its inactivation proceeds rapidly Contaminated streptomycin therefore should not be sterilized by heat but by passage through a Berkefeld Seitz or similar filter

Inactivation Streptomycin is not destroyed by micro-organisms as far as is known nor is it destroyed by body fluids pus or tissue juices It is not appreciably affected when subjected to a *p*H range of 2 to 9 but is decomposed by excessive acidity (such as 1 N HCl) or excessive alkalinity (such as 0 1 N NaOH)

Its action upon bacteria is neutralized by cysteine cevitamic acid and several ketone reagents by substances containing a carbonyl group by weak acids and by incubation in an anaerobic environment Certain sugars such as dextrose levulose and sucrose also inhibit the action of streptomycin presumably by the production of acids

Action upon Bacteria

Streptomycin is active against various gram positive and gram negative aerobic bacteria as shown in Table 16 It is relatively ineffective against anaerobic bacteria Perhaps the most striking effect of streptomycin as contrasted to penicillin is its action upon acid fast bacteria particularly *Mycobacterium tuberculosis*

From the standpoint of practical therapeutics one feature is of con siderable importance The concentration of streptomycin required to inhibit the organisms of a given species will vary widely from strain to strain For instance Buggs[3] found that some strains of *Escherichia coli* were sensitive to as little as 1 microgram of streptomycin while others were not inhibited by 256 micrograms

wise irregular and uncertain. It passes readily into the amniotic fluid and into the fetal circulation where the concentrations are approximately half as great as those in the maternal blood.

Excretion. Most of the streptomycin which reaches the blood is excreted in the urine. The amount excreted by this route varies from 50 to 90 per cent of a parenteral dose. According to Adcock[3] excretion occurs through the glomeruli. Urinary excretion of streptomycin is considerably slower than that of penicillin. As a result, streptomycin remains in the blood at fairly high levels for as long as twelve hours or more, depending upon the dose.

Six per cent or less of the streptomycin which reaches the blood is excreted by way of the feces, and the portion not excreted via the urine or the feces is apparently destroyed in the body.

Administration

Administration by Injection. Intermittent intramuscular injections are used most frequently for the systemic administration of streptomycin. Table 17 shows the blood concentrations which may be expected

TABLE 17

CONCENTRATION OF STREPTOMYCIN IN THE BLOOD AFTER INTRAMUSCULAR INJECTIONS

Dose (Grams)	*Mean Concentration for Three Hour Period* (Micrograms)	*Range of Concentration* (Micrograms)
0.1	2-3	
0.2	5-6	3-10
0.3	6-8	4-12
0.5	9-10	6-20
0.6	12-16	10-26

Based upon the report of the Committee on Therapeutics, National Research Council.[4]

after intramuscular injections of various doses. Since this antibiotic is not excreted so rapidly as penicillin, the interval between injections may be longer. An interval of three or four hours between injections is employed when the dose is 0.1 to 0.25 gm., and an interval of six hours when the dose is 0.5 gm. or more. If it is desired to maintain continuously high blood concentrations, however, the injections should be given every three hours no matter how high the dose.

Streptomycin can be dissolved in 1 to 5 cc. of distilled water or sodium chloride solution. The smaller the volume, the less the discomfort. Sodium chloride solution is less painful than distilled water. On the other hand, in vitro studies have shown partial neutralization of streptomycin by sodium chloride solution. Accordingly, it is best to administer

ical importance since bacteria often develop a tolerance for high concentrations of the antibiotic within a short period of time retaining at the same time all their former pathogenicity and virulence [9] Youmans[12] observed a thousandfold increase in resistance of tubercle bacilli in patients treated with streptomycin while Finland[5] reported that gram negative bacteria which were responsible for urinary tract infections developed a resistance more than four thousand times as great as that present before streptomycin therapy

Absorption Distribution and Excretion

Absorption Streptomycin is readily absorbed into the general circulation after intravenous intramuscular or subcutaneous administration After an intravenous injection the peak serum concentration is reached immediately and is followed by a progressive fall over the course of the next few hours After an intramuscular injection the peak concentration is not attained for an hour or longer and although this level is not so high as after an intravenous injection it is sustained longer After a subcutaneous injection the maximum concentration of streptomycin in the serum is achieved in two or three hours after which it falls gradually in the same way it does after an intramuscular injection

Up to the present writing no substance has been found which will delay the absorption of streptomycin after injection Oil and beeswax will not perform this function as they do for penicillin Fortunately as will be seen later streptomycin is excreted more slowly than penicillin so that the need for repository injections is not so great

After oral administration streptomycin is not absorbed into the blood in appreciable quantities It is not destroyed by the digestive juices but is excreted in the stools from which recovery of amounts as high as 98 per cent of the dose administered has been reported

Inhalation of nebulized streptomycin results in the absorption of only negligible amounts into the blood

Diffusion Streptomycin diffuses readily into many of the organs and tissues of the body It has been found in appreciable concentrations in the kidneys lungs and heart muscle whereas it was present in only small amounts in the brain and liver High blood concentrations are necessary to insure the passage of the antibiotic into the aqueous and vitreous humors of the eye Streptomycin is found in hepatic bile and in bile from the gallbladder when there is no obstruction in the cystic duct [13]

Some diffusion occurs into all the serous cavities In patients with peritonitis or ascites therapeutic concentrations of streptomycin have been obtained ordinarily after intravenous and intramuscular injections The levels attained in the pleural and pericardial cavities have not been so consistent Absorption into the cerebro spinal fluid is like

wise irregular and uncertain. It passes readily into the amniotic fluid and into the fetal circulation where the concentrations are approximately half as great as those in the maternal blood.

Excretion. Most of the streptomycin which reaches the blood is excreted in the urine. The amount excreted by this route varies from 50 to 90 per cent of a parenteral dose. According to Adcock[1] excretion occurs through the glomeruli. Urinary excretion of streptomycin is considerably slower than that of penicillin. As a result, streptomycin remains in the blood at fairly high levels for as long as twelve hours or more, depending upon the dose.

Six per cent or less of the streptomycin which reaches the blood is excreted by way of the feces and the portion not excreted via the urine or the feces is apparently destroyed in the body.

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Streptomycin can be dissolved in 1 to 5 cc. of distilled water or sodium chloride solution. The smaller the volume, the less the discomfort. Sodium chloride solution is less painful than distilled water. On the other hand, in vitro studies have shown partial neutralization of streptomycin by sodium chloride solution. Accordingly, it is best to administer

the antibiotic in distilled water unless this is too painful in which case isotonic sodium chloride solution may be used or 1 cc of 1 per cent procaine solution can be added to the streptomycin solution This anesthetic will diminish the pain without affecting the action of the antibiotic Intermittent intravenous injections are not used because the streptomycin is excreted rapidly and the method is wasteful Subcutaneous injections are not generally employed because of the pain which accompanies them Continuous intravenous infusions are seldom necessary because of the prolonged blood concentrations which are present after intramuscular injections When this route is employed 1 or 2 gm of streptomycin are dissolved in 1000 cc of isotonic sodium chloride solution and given slowly over the course of several hours

Oral Administration Only negligible amounts of streptomycin are absorbed into the circulation when the drug is given by mouth Since practically no destruction of the antibiotic occurs within the gastro intestinal tract it has been suggested that it may be employed to reduce the number of bacteria in the intestines before surgical operations and to combat intestinal infections Whether it will prove to be superior to the sulfonamides for these purposes remains to be determined Rutstein[10] found only a transitory reduction in the number of typhoid bacilli in the stools of carriers who were given streptomycin

Intrathecal Administration For the treatment of meningitis streptomycin should be given intrathecally as well as systemically Doses of 25 to 100 mg are employed dissolved in 5 to 10 cc of isotonic salt solution and injected at twenty four hour intervals after the withdrawal of a slightly greater amount of spinal fluid Injections may be made into the lateral ventricles or the cisterna magna as well as into the lumbar intrathecal space

Administration into Serous Cavities In order to insure adequate concentrations of streptomycin the antibiotic should be injected directly into the pleural peritoneal or pericardial cavities in cases where these cavities are infected with organisms which are streptomycin sensitive For this purpose the streptomycin is dissolved in isotonic salt solution in concentrations of 1 to 10 mg per cc, and injected in doses of 5 to 500 mg depending upon the sensitivity of the infecting organism

Inhalation Nebulized streptomycin may be administered by inhalation for bronchial and related infections Doses of 50 to 100 mg are dissolved in 1 to 2 cc of isotonic salt solution and inhaled at intervals of two to four hours The technique is similar to that employed for the inhalation of penicillin Since only negligible amounts of streptomycin are absorbed into the blood after inhalation we feel that the antibiotic should be given by injection for infections within the lung parenchyma or in the pleura

Administration by Other Routes Streptomycin in concentrations of 10 mg per cc may be used as nose drops or instilled into the conjunc

tiva The concentration used for instillation into the external auditory canal is 10 to 25 mg per cc and for local application in wounds is 0 2 to 0 5 mg per cc





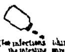




Fig 14 Procedures to be followed in the administration of streptomycin.

Toxic Reactions

Local Reactions Pain soreness and induration at the site of injection were observed more often with the early impure preparations than they are today Severe local pain may be relieved by the addition of 1 cc of 1 per cent procaine solution

When doses of 50 to 100 mg of streptomycin are injected intrathecally headache and vomiting or pain over the sacrum and the posterior parts of the thighs occasionally develop in some patients If the purer preparations are used reactions are encountered less frequently Doses above 100 mg produce severer reactions and should not be employed Repeated intrathecal instillations of streptomycin are usually accompanied by a pleocytosis up to 900 cells per cu mm [5]

Toxic Effects upon Cells or Organs In vitro and in animals the direct toxic effects upon cells have been few and usually slight As a result of experiments upon tissue cultures Heilman[6] concluded that the cytotoxicity of streptomycin is of about the same order as that of fairly pure penicillin tested by the same method Fatty changes in the liver and kidneys have been observed in animals after streptomycin administration but not in humans

Renal Damage Albumin and casts are frequently present in the urine of patients receiving streptomycin The casts are usually hyaline or granular occasionally cellular They are absent or minimal in neutral

or alkaline urines and frequent in acid urines Nitrogen retention and reduced renal function (as measured by the urea clearance test) are observed in a small percentage of individuals Renal irritation is usually of no importance and in the majority of cases the abnormal findings disappear soon after therapy is discontinued At least one instance has been reported[8] however in which fatal nephrosis was apparently produced by streptomycin

Streptomycin has been found to accelerate the coagulation of the blood of animals[7]

TABLE 18

TOXIC REACTIONS FROM STREPTOMYCIN THERAPY IN 1000 PATIENTS

	Number of Patients
Local reactions	
Local irritation	15
Tingling	2
Paresthesias	3
Cytotoxicity	
Albuminuria and casts	2
Neurologic disturbances	
Vertigo	33
Tinnitus	13
Deafness	6
Sensitization phenomena	
Rashes	49
Fever	49
Arthralgia	1
Histamine like effects	
Headache	55
Flushing of skin	43
Nausea and vomiting	1
Fall in blood pressure	1
Miscellaneous	
Diarrhea	1
Purpura hemorrhagica	1

Modified from the report of the Committee on Therapeutics and Other Agents National Research Council

Neurologic Disturbances Streptomycin frequently causes vestibular dysfunction When 1 to 2 gm a day are given the reaction generally appears[8] at the end of the fourth week at the end of the third week on a daily dose of 3 gm and during the second week on larger doses Labyrinthine dysfunction is manifested by vertigo a sensation of overshooting the mark when a sudden movement is made and ataxia all of which vary considerably in severity Nausea and vomiting may be present Nystagmus is infrequent The more pronounced symptoms usually diminish after a week to ten days even if streptomycin therapy is continued Milder symptoms will persist however for two to three months or may be permanent

Deafness appears in patients who are given unusually large doses in those who receive streptomycin intrathecally or in those who have pronounced renal insufficiency Significant improvement occurs in most patients after therapy is discontinued

Paresthesias of the face and of the extremities and diplopia have been observed occasionally

In order to prevent irreversible damage in the structures of the nervous system streptomycin should not be administered in doses exceeding 3 gm a day except for a short period of time or when larger doses are necessary to save life Whenever impairment of hearing or vestibular dysfunction occurs streptomycin therapy should be discontinued unless *further treatment is imperative*

Sensitization Phenomena Evidences of hypersensitivity to streptomycin have been observed in the form of fever skin eruptions arthralgia and eosinophilia Rashes and fever were observed in forty nine of the first 1000 patients treated (Table 18) These phenomena usually appear several days after the start of streptomycin therapy or on the first day of a second course *Rashes may be urticarial* erythematous or morbilliform or may resemble erythema nodosum Many of these phenomena are due to impurities present along with the streptomycin rather than to the antibiotic itself The disturbances of the eighth nerve described in the previous section may possibly be the result of sensitization to streptomycin

Histamine like Effects Impurities which affected patients in the same way as histamine were present in some of the early batches of streptomycin These produced headache flushing of the skin of the face and of the body nausea and vomiting These were usually transitory Under the control of the various manufacturers and of the Food and Drug Administration these have been almost entirely eliminated although slight reactions of this kind may still be encountered occasionally

Miscellaneous Reactions Diarrhea and purpura hemorrhagica were each observed in one out of 1000 patients Leukopenia has also been encountered It remains to be determined whether these reactions are related to streptomycin therapy or whether they merely occurred incidentally during the course of treatment

Indications for the Use of Antibiotics Sulfonamides and Specific Serums

Table 19 lists the therapeutic agents of choice for each of the bacterial infections Penicillin is preferred in pneumococcic streptococcic staphylococcic and gonococcic infections in anthrax and in *Streptobacillus moniliformis* infections It is used in conjunction with sulfonamides in pneumococcic and streptococcic meningitis and in meningococcemia and as an adjunct to specific serum in diphtheria and gas gangrene

Streptomycin is preferred in severe bacteremia or meningitis due to organisms of the coli aerogenes group in Klebsiella (Friedlander) infections *H influenzae* infections tularemia and tuberculosis It is effective

in urinary infections caused by gram negative bacilli although we have suggested that sulfonamides be used first because they are cheaper and

TABLE 19

RECOMMENDED CHOICE AMONG THE DIFFERENT THERAPEUTIC AGENTS FOR THE TREATMENT OF VARIOUS BACTERIAL INFECTIONS

	Penicillin	*Streptomycin*	*Sulfonamides*	*Specific Serum*
Pneumococcic infections				
Pneumonia	1		2	
Empyema	1			
Meningitis	1C		1C	
Streptococcic infections				
Beta hemolytic (except scarlet fever and meningitis)	1		2	
Scarlet fever	1			A
Meningitis	1C		1C	
Nonhemolytic (alpha and gamma)	1			
Staphylococcic infections	1			
Meningococcic infections				
Meningitis	A		1	
Meningococcemia	1C		1C	
Gonococcic infections	1	2	2	
Anthrax	1		2	
Rat bite fever caused by *Streptobacillus moniliformis*	1	A		
Typhoid fever		?		
Salmonella infections		?	?	
Shigella dysentery		?	1	A
Brucellosis		?	?	
Infections with organisms of the coli aerogenes group				
Peritonitis	1C	1C	1C	
Bacteremia		1	A	
Meningitis		1	A	
Urinary infections		2	1	
Klebsiella pneumoniae infections		1	A	
Hemophilus influenzae infections		1	A	A
Pseudomonas aeruginosa infections		1		
Tularemia		1		
Plague		?	1	
Glanders			1	
Tuberculosis		1		
Tetanus				1
Diphtheria	A			1
Gas gangrene	A			1
Botulism				1

Key
1 = *1st choice*
2 = *2nd choice*
1C = 1st choice combined with the other drug shown
A = recommended as an adjuvant in certain cases
= not recommended
? = value questionable

easier to administer Streptomycin is also effective in gonorrhea and in some cases of *Streptobacillus moniliformis* infection

Sulfonamides are preferred in meningococcic meningitis shigella dysentery plague and glanders They should be used in conjunction with penicillin in pneumococcic and streptococcic meningitis and in meningococcemia and as adjuncts to streptomycin in coli aerogenes Klebsiella and *H influenzae* infections They may be used instead of penicillin in pneumococcic pneumonia in many infections caused by beta hemolytic streptococci and gonococci and in anthrax

The use of specific serums is now limited almost entirely to the diseases in which bacterial exotoxins play a major part tetanus diphtheria gas gangrene and botulism Serums are still indicated as an adjunct to penicillin in certain cases of scarlet fever as an adjunct to streptomycin in *H influenzae* meningitis and perhaps in certain cases of shigella dysentery

The optimal method of treatment for peritonitis following perforation in the gastrointestinal tract has not been determined Combinations of penicillin plus sulfonamides or streptomycin seem to be best

For the three remaining diseases in the table—typhoid salmonella fevers and brucellosis—none of the currently available therapeutic agents is of proved value

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Part II

DISEASES CAUSED BY COCCI

7 Pneumococcic Infections

The pneumococcus (*Diplococcus pneumoniae*) is a lancet shaped gram positive coccus usually occurring in pairs and sometimes in short chains It is a normal inhabitant of the nose and throat of humans and is also a frequent incitant of the following diseases pneumonia meningitis otitis media and empyema It may also cause pericarditis endocarditis peritonitis arthritis conjunctivitis pyelitis localized abscesses of the skin and other rarer infections

The most important pneumococcic infection is pneumonia which will be considered in detail The other pneumococcic infections will be discussed either as complications of pneumonia or as separate diseases

Pneumonia

The pneumonias are a group of acute diseases involving the alveoli or the interstitial tissue of the lungs and are caused by a variety of infectious agents most frequently by one of the pneumococci Among 2500 cases of primary bacterial pneumonia observed by us the causative agents were

Diplococcus pneumoniae	98 1 per cent
Streptococcus hemolyticus	0 9
Klebsiella pneumoniae (Friedlander s bacillus)	0 6
Hemophilus influenzae	0 3
Staphylococcus aureus	0 1

In addition to the pneumonias caused by a specific micro-organism an indeterminate number are the result of a mixed infection by several bacteria Other varieties of pneumonia are caused by viruses and by rickettsial organisms

Pathologically there are three main varieties of pneumonia *lobar* lobular or bronchial and interstitial In lobar and bronchial pneumonia there is an outpouring of red blood cells and leukocytes into the alveoli making the affected portion of the lungs airless and firm In the lobar variety this process usually extends throughout an entire lobe or several lobes or it may extend part of the way across a lobe with a sharp fairly straight line of demarcation between the consolidated (i e airless) and the normal lung tissue In the bronchial variety there are one or

many patches of consolidation usually around the bronchi, a patch sometimes involving a lobule or several lobules. The distinction between lobar and bronchial pneumonia is not always definite, however, as it is not uncommon to find the lobar form of consolidation involving one lobe and patches of bronchopneumonia elsewhere. In lobar pneumonia the lower lobes are most frequently affected, although any lobe or combination of lobes may be involved. In the interstitial form the consolidation is patchy, and under the microscope the areas around the bronchi and the alveolar walls are seen to be infiltrated with leukocytes, often mononuclear in type. Pneumococci cause practically all cases of lobar pneumonia. Most of the cases of bronchopneumonia are likewise caused by pneumococci and the remainder by other bacteria. Interstitial pneumonia usually results from infections with the viruses.

Pneumococcic Pneumonia

Pneumococcic pneumonia is in reality a group of diseases caused by various types of pneumococci, about seventy-five in number. Only thirty-one of these types (I through XXXIII, excluding XXVI and XXX) are regularly identified by typing in the average hospital or public health laboratory, and only about eight or ten types are encountered with any degree of frequency. Table 20 gives the distribution of types among patients with pneumonia. Types I, III, VII, VIII and II predominate in adults in that order, while types XIV, I, VI and XIX are most frequent in children.

TABLE 20

TYPE DISTRIBUTION OF PNEUMOCOCCIC PNEUMONIAS IN ADULTS AND CHILDREN (COLLECTED FROM VARIOUS SOURCES)

	Incidence (Per cent)				
Type	Adults	Children	Type	Adults	Children
I	22.0	14.1	XVII	[illegible]	1.4
II	7.4	[illegible]	XVIII	2.5	9
III	12.8	3.9	XIX	2.4	8.2
IV	7	4.6	XX	1.6	1.4
V	6.6	4.9	XXI	0.6	1.6
VI	2.8	12.3	XXII	0.9	1.5
VII	9.3	4.0	XXIII	0.7	3.0
VIII	8.0	1.4	XXIV	0.6	0.7
IX		1.6	XXV	1.1	0.03
X	1.1	0.8	XXVII	0.3	0.003
XI	1.1	1.6	XXVIII	0.4	0.9
XII	1.6	0.4	XXIX	0.8	1.3
XIII	1.1	0.9	XXXI	0.3	0.7
XIV	4.1	17.2	XXXII	0	0.01
XV	0.9	8	XXXIII	0	0.5
XVI	0.8	1.4			
Total Number of Cases				14,996	865

Most frequent types shown in bold face type

Pneumococcic pneumonia is encountered more frequently in males than in females Sixty three per cent of our patients were males The disease affects persons in all age groups but is particularly prevalent during the prime of life Among our adult patients 68 per cent were between the ages of twenty and forty nine years

SYMPTOMS AND SIGNS

About 60 per cent of patients with pneumococcic pneumonia have symptoms of a cold preceding the onset of the pneumonia The disease itself usually begins abruptly often with a shaking chill followed by fever or with pleural pain or both Chill and chest pain are called cardinal symptoms Another cardinal symptom is cough with expectoration of blood stained sputum

Among 1000 patients with pneumococcic pneumonia observed by us 655 experienced a chill 863 had pleural pain and 521 expectorated sputum which contained blood in some form Occasionally the patient gives no indication of the cardinal symptoms but there is almost invariably a point in the history of an upper respiratory infection when the patient definitely became worse Either chilly sensations or fever began at that time or dyspnea and cough became pronounced Thus the time of the onset can practically always be learned with certainty

The *chill* occurring at the onset of pneumonia is usually a severe rigor There is ordinarily only one seldom more than two Chilly sensations may be present instead of a shaking chill The *pleural pain* is characteristically sharp and stabbing or cutting in character worse on breathing or coughing If pain is induced or aggravated by respiration there may or may not be pain when the patient moves about in bed but pain on movement is not present unless there is pain on breathing also The pain is more frequently felt over the lower back or in the axilla but may be present anywhere over the chest Pleural pain may be referred from the diaphragm to the abdomen to the flank or to the areas above either clavicle along the side of the neck or on the ridge of the trapezius Pleural pain when present usually starts at or soon after the inception of the pneumonia and disappears soon after the patient begins to improve Sometimes it appears during the course of resolution in which event it is usually transitory and less severe

The *sputum* typical of pneumonia is pink mucoid and tenacious early in the disease becoming rust-colored within a day or two and later green or yellow and purulent There are however many variations blood may be streaked in the sputum and be thoroughly mixed with it or may give it a prune-juice color In some cases the sputum shows no trace of blood at any time Occasionally the sputum may be yellow because of jaundice or because small amounts of blood are changed to acid hematin

The *temperature* usually rises to between 103 and 105° F within a

few hours after the onset and remains high in untreated cases until the fever terminates by crisis or rapid lysis The diurnal variation in the temperature during the fastigium is seldom more than 2 degrees F The beginning of crisis or lysis may occur at any time up through the fourteenth day or even later but is most common between the fifth and ninth days after the onset Since the sulfonamides and penicillin have been used universally *one practically never sees a spontaneous crisis*

Dyspnea is usually present at the height of the disease When much pleural pain is present respirations may become still more rapid and also shallow An expiratory grunt is frequently audible and when present is helpful in the diagnosis Vomiting may occur especially in children Abdominal distention is a frequent accompaniment of severe pneumonia Diarrhea is rare Delirium is seen in a great many cases and may be due to the toxemia of the disease to anoxemia to alcoholism (delirium tremens) to meningitis or to sulfonamides administered for treatment Convulsions occur frequently in children but seldom in adults unless they are alcoholics or epileptics

The *typical pneumonia patient* breathes rapidly and distressfully with an expiratory grunt His nostrils dilate with each inspiration his lips are dry and covered with herpes His lips ear lobes and nailbeds are cyanotic His face is flushed his skin hot and dry Examination of the chest after the disease is well under way reveals in most instances the signs given in Table 21 In some cases the typical signs of consolida*tion may be present only for a day or two In rare instances they do not* appear at any time Instead of the typical signs of consolidation any of the following features may be elicited breath sounds absent or tubular but distant voice sounds diminished or absent altogether or coarse and sibilant rales present throughout the disease Resolution usually begins around or soon after the drop of temperature which heralds the beginning of the crisis or lysis and is usually complete within two or three weeks although in an occasional patient it may take several weeks or even months for the consolidation to disappear entirely

Cardiovascular System There is seldom any perceptible change in the heart size although some observers claim that careful roentgenographic studies will demonstrate a slight increase in the majority of instances The first sound often approaches the second in quality and the second pulmonic sound is usually increased *in intensity* The pulse rate is increased although not out of proportion to the temperature except in the most toxic cases After the temperature falls the pulse rate in an occasional patient may drop into the fifties or even lower Premature systoles are occasionally present during the disease Other irregularities such as auricular fibrillation and flutter are encountered less often The blood pressure remains at its usual level or drops slightly in the average patient although it may fall considerably in the severely patient

Gastrointestinal System Abdominal distention due to tympanites is always present to some degree It usually disappears soon after the temperature falls Jaundice is evident *in an occasional patient but is* more frequent in Negroes

TABLE 21

SIGNS OBTAINED ON PHYSICAL EXAMINATION OF THE LUNGS IN THE DIFFERENT STAGES OF PNEUMOCOCCIC PNEUMONIA

Stage of Disease	*Percussion*	*Breath Sounds*	*Auscultation*		*Adventitious Sounds*
			Voice Sounds		
			Whispered	Spoken	
Early	No change or slight dullness	Diminished sometimes faint tubular	May be increased	Usually normal	Often a few fine rales occasionally a pleural rub
Height of of disease	Dullness or flatness	Tubular	Increased	Increased with change in quality	Fine and medium rales sometimes a pleural rub
Resolution	Dullness gradually decreasing	Tubular becoming bronchovesicular and then normal	Normal	Normal	Medium and large mucous sibilant and sonorous rales

LABORATORY AND X RAY EXAMINATIONS

The *leukocyte count* is usually elevated to between 12 000 and 30 000 *per cu mm but it may remain within normal limits or may rise to* 50 000 or more The count cannot be correlated closely with the severity of the disease except that in the mildest cases there is only slight elevation while a white blood cell count below 5000 or above 10 000 means a poorer prognosis than the average The granulocytes usually comprise *from 80 to 95 per cent or more of the leukocytes There is a shift to the* left in the granulocytic cells with an increase in the band forms and metamyelocytes and sometimes the appearance of a few myelocytes This is usually true even when the total leukocyte count does not rise above normal limits In most cases the granulocytes contain numerous toxic granules

The *sputum* should be typed whenever possible A specimen which has just been coughed up is preferable When the patient is not coughing or is swallowing sputum as is *often the case with children and comatose* patients a specimen may be obtained by inserting a rubber tube attached to a syringe into the pharynx as far as the epiglottis and applying suction Other alternatives are (1) taking a culture from the nasopharynx and placing it in a special glucose-blood broth medium or (2) aspirating

the gastric contents and typing one of the flecks of sputum which are usually found floating on top

Typing of pneumococci is done by the Neufeld method which is based on the principle that swelling of the capsular substance occurs when pneumococci are placed in the rabbit antiserum of the corresponding type but not in the presence of serums of other types If a type is not found or if confirmation is desired sputum is injected into the peritoneal cavity of a mouse and the peritoneal exudate or a culture of the brain or of the heart s blood is typed by the Neufeld or by an agglutination method

Pleural cerebrospinal pericardial and other fluids obtained from pneumonia patients should always be cultured and typed These fluids are often the most important means of identifying the significant pneumococcus type or they may reveal a different micro-organism as the cause of the complication

A *blood culture* is a procedure of great importance in evaluating the severity of pneumonia The percentage of patients suffering from pneumococcic pneumonia found to have positive blood cultures varies from 15 to 30 per cent depending upon the techniques used the number of cultures taken and the severity of the disease As will be shown in the section on Prognosis under all forms of treatment the fatality rate is higher in patients from whose blood pneumococci can be cultured

Frisch[6] has devised a simple test which merits more attention than it has received It consists in counting the number of extracellular pneumococci per oil immersion field in a stained smear of sputum The organisms in ten widely separated fields are counted The relation of the number of pneumococci to the prognosis is as follows 10 or less per field prognosis excellent 11 to 35 good 36 to 65 fair more than 65 poor

X *ray* changes in the lungs may appear as early as four or five hours after the onset and almost always within the first twenty four hours In lobar pneumonia an area of increased density may appear first at the hilum or at the periphery spreading progressively from either place to occupy one or more lobes The time required for maximal involvement as shown by x ray is more than three days in the majority of cases and may be as long as six days [7] Sometimes roentgenograms do not show complete consolidation at any time during the course of the disease but reveal only a faint graying or ground glass appearance of the involved area X ray evidence of consolidation usually appears at the same time as the earliest physical signs If one appears ahead of the other the roentgenograms are likely to be abnormal first Occasionally the converse is true

X ray evidence of resolution first becomes apparent anywhere from the second to the thirteenth day of the disease or later In about half of the cases the physical signs and the x ray evidence of consolidation disappear at the same time In one fourth of the patients the physical

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Aspiration Pneumonia In debilitated or stuporous patients and in patients during operation or delivery food vomitus or other material may be aspirated into the bronchi The resulting irritation often allows the carrier type pneumococci or other organisms which accompany this material to set up an inflammation A special variety of this condition known as oil aspiration pneumonia may follow the use of oily nose drops or the drinking of mineral oil by debilitated persons

Postoperative Pneumonia After surgical operations especially those in the upper abdomen elevation of the diaphragm occurs resulting in diminished respiratory excursions and diminished vital capacity Furthermore mucus or vomitus may be aspirated into the bronchi where the diminished cough reflex allows it to remain and become viscid Any of these conditions may result in areas of atelectasis varying in size from tiny lobular patches to entire lobes Such atelectatic areas form excellent locations for bacteria (usually carrier type pneumococci or the mixed flora of the respiratory tract) to proliferate and cause pneumonia

Post-Traumatic Pneumonia A nonpenetrating injury of the chest is sometimes followed by pneumonia directly beneath the site of the trauma or at the site of contrecoup pulmonary injury This subject has been excellently reviewed by Phillips [11] to whose article the interested reader is referred

DIAGNOSIS

The diagnosis of pneumonia in typical cases is usually easy Much importance should be attached to the history If two or all three of the cardinal symptoms (chill followed by fever pain in the chest and cough with the expectoration of blood tinged sputum) are present pneumonia may be considered likely even if abnormal physical signs are not found at first In such an event a roentgenogram of the chest will usually reveal the infiltration or the sputum may be typed immediately by the Neufeld method The finding of a type I II V or VII pneumococcus makes the diagnosis almost completely certain since these types are seldom found in carriers The presence of one of the other types of pneumococci is not diagnostic of pneumonia although this finding contributes evidence in favor of its presence If the leukocyte count is elevated with a shift to the left of the cells of the granulocytic series the diagnosis *is further strengthened*

In the bronchopneumonias one sees the most varied pictures and consequently has the most difficulty with the diagnosis In many cases the insidious approach of the disease especially during the course of some other illness such as congestive heart failure bronchiectasis asthma or during convalescence from an operation the paucity of symptoms of the pneumonia and the frequent lack of any signs other than scattered rales all combine to defy an accurate diagnosis If there is no change in the

signs are the last to leave and in the other one fourth the roentgenogram remains abnormal longer

SPECIAL FORMS OF PNEUMONIA

Pneumonia in Children In addition to the fact that it is often caused by types of pneumococci which are not the most frequent etiologic agents in adults pneumonia in childhood differs in other important respects In children up to and including two years of age bronchopneumonia is relatively more frequent than in adults Convulsions and vomiting may be early symptoms Sputum is usually swallowed The case fatality rate is lower than in adults although not so low as in older children

In children aged three to twelve years the lobar form is about as frequent as in adults Convulsions vomiting diarrhea delirium and meningismus are more common than in adults The fatality rate is low being about 2 per cent even without specific treatment

Pneumonia in the Aged By the time they have reached the age of fifty years many people have developed certain irreversible changes in the respiratory organs such as emphysema and bronchiectasis and in the circulatory system such as arteriosclerosis of the aorta the coronary arteries and the arteries to other vital organs All these factors combine to make older people less resilient The difficulty which the elderly patient experiences in adjustment to a severe infectious disease is especially evident in pneumonia Furthermore in elderly patients those mechanisms by which the host fights disease such as elevation of temperature and leukocytosis may be diminished or absent These and other factors cause the case fatality rate in adults to rise progressively with age as shown in Table 26 (p 121) regardless of the kind of treatment given

Bronchopneumonia is relatively more frequent in older than in younger individuals and more older patients have bacteremia The types of pneumococci considered to be carrier types (III IV VI and those above VIII) cause a proportionately higher percentage of cases

An insidious onset often characterizes pneumonia in the aged Chills or the other cardinal signs are less frequent than in young people Fever may be low grade or may be absent altogether These and other features of pneumonia in patients past sixty have been well reviewed by Zeman [19]

Hypostatic Pneumonia This is a form of pneumonia which is particularly likely to occur in older patients especially in those who have been lying in bed for some time with a minimum of movement Slowing of the pulmonary circulation in these people results in exudation of fluid into the alveoli in the bases of the lungs and consequently the carrier type pneumococci and other carrier organisms multiply and produce patches of pneumonia

the patient is suffering from a condition which might be a predisposing cause for infarction of the lung (congestive heart failure peripheral or pelvic venous thrombosis or an operation) this diagnosis should be suspected In general in pulmonary infarction the temperature and leukocyte counts are lower and the patient after the first period of shock if this occurs is not so toxic as in pneumonia Even the roentgenogram may fail to differentiate these two conditions In such cases it is wisest for the physician to treat the patient for pneumonia being prepared meanwhile to re-evaluate the situation at any moment if further information becomes available

Acute bronchitis or *tracheobronchitis* is characterized by cough with no sputum or with the expectoration of mucoid or mucopurulent sputum which may occasionally be blood tinged (although we have never observed a rusty or prune-juice color) The temperature seldom rises above 102 5 F but may occasionally be higher The same is true of a leukocyte count above 11 000 or 12 000 per cu mm Substernal tightness and pain often appear but pleural pain is rarely present without some pneumonia Mucous and sibilant rales comprise the maximal physical signs Toxicity and cyanosis are not present

Pulmonary tuberculosis may simulate pneumonia especially when it is fulminating Chills are infrequent in tuberculosis the sputum may be bloody but not rusty the lesion is seldom unilateral if it is large enough to cause much toxicity the fever is usually irregular and leukocytosis is infrequent X ray evidence of cavities may be present in tuberculosis Whenever the disease is suspected frequent examinations of the sputum for tubercle bacilli should be made

Acute miliary tuberculosis is another form of the disease which may be mistaken for pneumonia The fever is usually sustained at a high level although it may be irregular The leukocyte count may be moderately elevated within normal limits or slightly lower Definite signs of consolidation are not present although diffusely scattered rales are often heard A roentgenogram of the lungs which shows the miliary lesions or the finding of tubercle bacilli in the sputum is necessary for a definite diagnosis

Congestive heart failure is confused with bronchopneumonia because cyanosis dyspnea and rales may be present in either disease The low grade fever which sometimes occurs in patients with heart failure is considered to be due to pulmonary infarctions The decision as to whether a small patch of pneumonia is present in the congested lungs of a patient with heart disease is difficult and at times impossible to make The presence of high fever of leukocytosis (above 12 000 per cu mm) or of pneumococci belonging to types I II V or VII in the sputum would point to pneumonia If none of these is present treatment should be directed toward improvement of the cardiac status If a small patch of pneumonia does happen to be present it is of minor importance if it

underlying disease to account for the change in its course if there is persistent fever if the leukocyte count is increased above 15 000 per cu mm or if there is a shift to the left in the granulocytes the diagnosis may be tentatively made Areas of consolidation should be searched for diligently They may be obscured by rales originating in the bronchi The x ray finding of consolidation will be helpful although patches of consolidation similar to those appearing in bronchopneumonia may occur in other pathological conditions particularly when scattered pulmonary infarcts or small areas of atelectasis are present When there is good reason for the physician to suspect bronchopneumonia he should proceed with specific treatment since he may never obtain the complete evidence upon which to make a diagnosis

Differential Diagnosis In considering the diagnosis it is necessary to learn first whether pneumonia of any kind is present and second

TABLE 22

FINAL DIAGNOSIS ON 200 PATIENTS IN WHOM PNEUMONIA WAS ERRONEOUSLY DIAGNOSED WHEN THEY WERE FIRST SEEN

Final Diagnosis	*Number of Patients*	*Final Diagnosis*	*Number of Patients*
Pulmonary infarction	36	Postoperative or postdelivery atelectasis	12
Acute bronchitis	29	Acute miliary tuberculosis	11
Pulmonary tuberculosis	21	Bronchial asthma	10
Congestive heart failure	18	Bronchiectasis	[illegible]
Lung abscess	15	Myocardial infarction	3
Pluerisy (dry or with effusion)	1	Acute pericarditis	3
Influenza	11		

Renal calculus Typhoid fever Fever of undetermined etiology 2 each
Spontaneous pneumothorax Acute cholecystitis 1 each

whether the pneumonia is pneumococcic in origin or due to other organisms

Table 22 shows the final diagnosis in 200 patients whose illness simulated pneumonia when first seen Other respiratory diseases such as pulmonary infarction acute bronchitis pulmonary and miliary tuberculosis and lung abscess were frequently confused with pneumonia Among the nonrespiratory diseases congestive heart failure led the list although acute pericarditis and myocardial infarction frequently exhibited confusing features

Pulmonary infarction is most commonly mistaken for pneumonia Although the onset has long been described as sudden with sharp pain in the chest cough and the expectoration of blood streaked or bloody sputum the disease often makes its insidious appearance as fever which may or may not be accompanied by chest pain and cough Whenever

becomes larger one should find evidence of its presence in time to initiate treatment

Solitary *abscess of the lung* sometimes resembles pneumonia in that it may start suddenly with fever pain in the chest and cough and may be accompanied by the expectoration of blood tinged sputum More often however there is a history of a tonsillectomy or of foreign body aspiration preceding the disease and the onset is gradual The sputum is purulent and contains only streaks of blood if any The physical signs in the chest while they may occasionally be the typical signs of con solidation are usually characterized by large mucous rales The leukocyte count is usually elevated in both conditions although it seldom rises above 15 000 in lung abscess In many cases one must rely upon the x ray picture to show the typical excavation of lung abscess

When there is a *dry pleurisy* without any signs of consolidation the clinician cannot be sure that he is not listening to a pneumonia in its early stages The presence of a definite chill of high fever of leukocytosis or of the typical pneumococcic sputum would be in favor of pneumonia When pleurisy with effusion is present dullness and the absence of breath and voice sounds over the involved area are of course the characteristic physical signs but confusion arises because of the fact that they may also be found over an area of pneumonia either when it is accom panied by effusion or even in the absence of fluid High fever toxicity leukocytosis and sputum especially if characteristic would favor the diagnosis of pneumonia

Influen a or *grip* is seldom accompanied by chill pleural pain or the sputum characteristic of pneumonia Rales when present are of the kind found in bronchitis A leukocyte count above 11 000 or 12 000 is rare in uncomplicated influenza while there is often a leukopenia

Atelectasis which occurs after an operation or after delivery usually takes place within the first few hours The patient may be quite dyspneic and cyanotic but seldom has much fever or leukocytosis A roentgenogram often shows narrowing of the interspaces and elevation of the diaphragm on the affected side sometimes accompanied by a shift of the mediastinum to that side

Other conditions such as bronchiectasis pulmonary neoplasm myocardial infarction acute pericarditis renal and gallbladder colic acute appendicitis (especially in children) spontaneous pneumothorax and the febrile diseases such as typhoid and typhus fevers and malaria usually can be readily differentiated if roentgenograms and proper laboratory procedures are utilized as indicated

If pneumonia is present the etiologic variety should be determined Primary atypical pneumonia of unknown etiology (so-called virus pneu monia) is more frequently encountered than any of the other nonpneu mococcic pneumonias The chief characteristics which differentiate it from pneumococcic pneumonia are given in Table 23 The onset is abrupt

in 75 per cent of the cases of pneumococcic as compared with 30 per cent of primary atypical pneumonias Chills occur in nearly two-thirds of the patients with pneumococcic pneumonia and most of the remainder

TABLE 23

DIFFERENTIAL DIAGNOSIS OF PNEUMOCOCCIC AND PRIMARY ATYPICAL PNEUMONIAS

	Pneumococcic	*Primary Atypical*
Onset	Usually sudden	Usually gradual
Chill	Usually one occasionally two	Usually chilliness occasionally a chill
Chest pain	Pleural	Retrosternal on coughing
Cough	Usually loose	Usually dry and paroxysmal in first part of illness
Sputum	Usually rusty or prune juice may be bloody blood streaked or purulent	Usually mucoid Occasionally blood-streaked
Malaise headache and general aches	Rare	Frequent
Labial herpes	Frequent	Rare
Fever	Usually continuous	Remittent or irregular
Pulse rate	Consistent with degree of fever	Often slower than expected according to amount of fever
Physical examination of lungs	Signs of consolidation usually appear early	Rales early sometimes signs of consolidation later
X ray of lungs	Usually consolidation of one or more lobes	Infiltration may be hilar or extend from hilum into a base or patchy in several lobes
Leukocyte count	10 000 to 40 000 in most cases	Usually below 10 000 Occasionally as high as 15 000 late in disease
Cold agglutinins	Rarely positive	Often positive in moderately or severely ill patients
Sputum typing	Pneumococci can be typed from 98 per cent If pneumococci I II V and VII present they are usually the cause	Occasionally pneumococci Type III or higher types
Blood culture	Pneumococci in 15 to 50 per cent	Sterile

have a chilly sensation at the onset followed by a feeling of warmth while most of the patients with primary atypical pneumonia have intermittent sensations of chilliness but infrequently an actual chill Chest

pain occurs in 86 per cent of the patients with pneumococcic pneumonia and has the characteristic location of pleural pain while the pleura is rarely involved in primary atypical pneumonia Characteristic pink or rusty sputum is present in over half of the cases of pneumococcic pneumonia but if blood is present at all in primary atypical pneumonia it consists of streaks in the sputum Malaise headache general aching and sore throat are frequent in primary atypical and rare in pneumococcic pneumonia On the other hand herpes labialis is characteristic of the latter disease Fever in pneumococcic pneumonia usually reaches a high level and remains there while in primary atypical pneumonia it is irregular or remittent The pulse rate which usually rises concomitantly with the temperature in pneumococcic pneumonia is likely in the primary atypical variety to be slower than the height of the temperature would lead one to expect

The physical signs of pneumococcic pneumonia have been discussed in detail on page 105 In the early stages of primary atypical pneumonia, or throughout the entire course in mild cases physical signs may be absent or may consist of a few mucous rales Rales usually become more abundant later and definite signs of consolidation may appear Throughout the course the physical signs usually remain less extensive than the roentgenographic infiltration The latter is characteristic in most instances usually starting at the hilum and extending into the periphery most often in the lower lobes Sometimes there are soft mottled areas of infiltration in several lobes Only occasionally is there a dense infiltration similar to that found in lobar pneumonia

In pneumococcic pneumonia the total leukocyte count is below 10 000 in about 6 per cent of the patients and above 20 000 in nearly two-thirds of all cases In primary atypical pneumonia on the other hand the leukocyte count rarely exceeds 10 000 per cu mm during the first few days of the disease Later it may reach 11 000 to 15 000 in about one-fourth of the patients The cold agglutination test may be helpful in diagnosis since cold agglutinins are usually present in patients with moderate or more severe primary atypical pneumonia and rarely present in pneumococcic pneumonia Sputum should be obtained for typing whenever the etiology of the pneumonia is in doubt and in severely ill patients the blood should be cultured The presence of pneumococci in the blood or of types I II V or VII in the sputum is almost certain evidence of pneumococcic pneumonia

Pneumonia due to the ornithosis virus is similar in its clinical characteristics to a severe case of primary atypical pneumonia Diagnosis is made on the basis of the clinical features the history of a recent contact with sick parrots or other sick birds and the identification of the virus by inoculation of mice with the patient s sputum

Bacterial pneumonias other than pneumococcic are usually diagnosed by examination of the sputum and by blood culture There are also

certain distinguishing clinical characteristics Pneumonia caused by hemolytic streptococci is accompanied by marked prostration toxicity and cyanosis and sometimes by presternal pain and hoarseness

Pneumonia caused by *Klebsiella pneumoniae* (Friedlander s bacillus) occurs especially in older people is often gradual in onset and is usually severe and prolonged Leukocytosis is not so frequent as in pneumococcic pneumonia and the count seldom goes above 20 000 per cu mm when it occurs The sputum is unusually mucoid and tenacious

Staphylococcic pneumonia is often secondary to an infection caused by these organisms elsewhere in the body In other cases it is a sequel to influenza The sputum is blood tinged or buff salmon pink or chocolate colored The patients are toxic and prostrated Roentgenograms reveal a bronchopneumonic type of consolidation often with abscess formation

Hemophilus influenzae pneumonia is not easily distinguished except by identification of the organisms in the sputum or blood It occurs especially in infants and children Consolidation is more likely to be patchy than lobar The leukocyte count is below or within normal limits or slightly elevated

PREVENTION

Although pneumococcic pneumonia is not a highly contagious disease it is sometimes transmitted to an attendant or to another member of the family Accordingly the isolation precautions outlined on page 23 should be followed The use of sulfonamides or penicillin for prophylaxis is not recommended since there is no definite evidence that these procedures will prevent the development of pneumonia Furthermore the administration of these drugs may result in the appearance of sulfonamide-resistant* or penicillin resistant strains of pneumococci in the respiratory passages of normal individuals Vaccines made from whole pneumococci and the specific carbohydrates of pneumococci will produce immunity but their prophylactic value is limited because the immunity is specific for only a single type of pneumococcus

TREATMENT

General Treatment The patient with pneumonia should be put to bed and kept there He should be recumbent or propped up in a partial sitting position whichever allows him to breathe more easily He should be kept warm whil being allowed a reasonable quantity of fresh air Care must be taken during feeding bathing and other procedures to see that he is not exposed to the cold or allowed to exert himself Sleep and rest should not be disturbed except when absolutely necessary When the temperature pulse and respiratory rates have fallen to normal levels either as a part of the natural course of the disease or after specific therapy and all physical and roentgenologic signs of pneumonia are gone the patient may start to get up

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Heart failure occurs rarely in patients with pneumonia and then only if they have had preexisting heart disease If true congestive heart failure or auricular fibrillation is present it should be treated just as it would be under any other circumstances but the routine administration of digitalis to all patients with pneumonia is to be condemned as a practice which does no good and may do harm The vascular failure which occurs in patients with severe pneumonia is considered to be peripheral Methods of combating this state are discussed on page 17

Diarrhea should be checked by means of opiates Hiccup usually stops if a carbon dioxide-oxygen mixture is administered in a closed system (Breathing in and out of a paper bag makes a satisfactory improvisation for home use)

Penicillin Therapy The pneumococcus is among the organisms susceptible to penicillin When this antibiotic is given to patients with pneumococcic pneumonia morphologic changes in the organisms obtained in the sputum are often apparent within the first twelve or twenty four hours after the initiation of treatment Ory[10] found that pneumococci disappeared from the sputum of 87 per cent of his patients while they were under treatment with penicillin

Penicillin has now been used in a sufficient number of patients to establish the fact that it is the drug of choice for the treatment of pneumococcic pneumonia Its administration should be started as soon as the physician is reasonably sure of the diagnosis of pneumonia and after sputum and blood have been collected for typing and culture It may be given orally in doses of 75 000 to 100 000 units every three hours intramuscularly in oil and beeswax in doses of 300 000 units every twelve hours or intramuscularly in aqueous solution 15 000 units every three hours When doses every three hours are being given we feel that they should be continued throughout the twenty four hour period even though Tillett[16] obtained good results by giving only four injections during the day and omitting those at night

Among 262 cases in which we calculated the time required for the temperature to drop it fell and remained below 101 F in 52 per cent within twenty four hours after penicillin therapy was started Forty eight hours after the initial dose the temperature had fallen below 101 F in 77 per cent of the patients Such a high frequency of crisis or rapid lysis is the common experience of clinicians treating pneumonia with penicillin although in an occasional patient the temperature takes several days to fall Temperature charts showing the typical response of patients to treatment with penicillin are shown in Figures 15 and 16 The pulse and respiratory rates may be expected to fall and the other evidences of toxicity to recede along with the drop in temperature

Penicillin should be administered until the temperature has remained below 100 F for three days It may then be stopped provided that the signs of toxicity have disappeared and there are no purulent compli

The diet should be easily digestible but high in calories and composed of bland mostly carbohydrate foods A large part of the diet may be in fluid form since the fluid intake should be kept up to 3000 cc a day

Symptomatic Treatment Cough is rarely distressing in itself but may need to be suppressed because it disturbs rest or aggravates the pleural pain Codeine in doses of 0 03 to 0 06 gm (½ to 1 grain) in adults and proportional amounts in children is usually sufficient

Pleural pain frequently gives trouble and may be excruciating If the pain is in the region of the ribs the intercostal nerves affected may be blocked between the area of the pain and the vertebral column by the subcutaneous injection of a small amount of 1 or 2 per cent procaine solution The pain will disappear within a few minutes after the injection and remain absent for several hours or may not return at all If the pain reappears the procedure may be repeated

The pain can often be decreased by strapping the chest with adhesive or by the application of a binder In our experience this method is inferior to the employment of procaine since it seldom gives complete relief and is at the same time bothersome to the patient Furthermore if the pain is referred to the abdomen or above the clavicle indicating that the diaphragmatic pleura is affected strapping or binding will do no good and may indeed make the condition worse by increasing the activity of the diaphragm

If the procaine block cannot be used or is unsuccessful codeine in doses of 0 03 to 0 06 gm (½ to 1 grain) or morphine 0 008 to 0 01 gm (⅛ to ⅙ grain) may be given Large doses of morphine are not advised because they may depress the respiration too much If it is used wisely at strategic moments morphine may give immeasurable comfort to the patient ill with pneumonia If it is given in too large doses it may be the factor precipitating death A routine order for morphine at regular intervals should never be written

Abdominal distention should be detected when the first evidences appear and steps should be taken immediately to combat it If relief is not complete a rectal tube may be inserted and at the same time an electric pad or turpentine stupes placed on the abdomen When distention is persistent these measures should be combined with the subcutaneous injection of 0 5 to 1 0 cc (7½ to 15 minims) of pitressin The inhalation of 95 per cent oxygen often brings about relief of this symptom

Anoxia manifests itself most commonly by cyanosis Other evidences of its presence are rapid respiration a rapid pulse rate without any other cause or marked restlessness When there is the slightest suspicion of oxygen deficiency it is best to begin oxygen administration The only disadvantage of this type of therapy is the fact that confining the patient within a tent often frightens him while a catheter or face mask may annoy him and disturb him The methods of administration are given on pages 18 to 21

units every two hours should be given or 600 000 units in oil and beeswax may be administered at twelve-hour intervals. Oral treatment should not be depended upon under these circumstances. We might add, however, *that in our experience it is seldom necessary to change from the* oral to the intramuscular route or to increase the doses recommended for routine use. The majority of patients will recover promptly when given these doses. In rare instances a shift to sulfonamides may be indicated because of pronounced resistance of the infecting pneumococcus to penicillin.

Sulfonamide Therapy. The fall in temperature when sulfonamides are employed is similar to that resulting from penicillin therapy. We studied 375 cases from this standpoint and found that the temperature fell and remained below 101° F. within twenty-four hours after the initial dose of sulfadiazine in 51 per cent of the patients and within forty-eight hours in 72 per cent.

TABLE 24

RESULTS OF TREATMENT IN PNEUMOCOCCIC PNEUMONIA

Kind of Treatment	*Number of Patients*	*Died*	
		Number	Per cent
No specific treatment	8101	2473	30.5
Specific antipneumococcic serum	9053	1345	14.9
Sulfonamides (with or without serum)	24714	2585	10.5
Penicillin (with or without sulfonamides)	8?0	4	5.7

From Finland.

As shown in Table 24, among the patients with pneumococcic pneumonia who did not receive specific treatment, 30.5 per cent died. When type specific antipneumococcic serum was given, the case fatality rate was 14.9 per cent. With the use of sulfonamides plus specific serum in some cases where it was needed, the case fatality rate was reduced to 10.5 per cent. Penicillin alone or in combination with sulfonamides brought the fatality rate down to 5.7 per cent. Table 25 demonstrates that the percentage of serious complications was significantly less among our patients treated with penicillin than among those treated with sulfonamides.

Obviously penicillin is the drug of choice since it gives better results and has the added advantage of causing fewer toxic reactions. On the other hand, most patients will do just as well on sulfonamide treatment and at the present time the sulfonamides are much cheaper than penicillin. If the latter drug continues to be costly, sulfonamides may be given routinely where expense is an important factor, with the understanding that penicillin will be substituted if the patient does not improve within twenty-four to forty-eight hours or develops a serious toxic reaction at

cations When penicillin therapy is discontinued too soon the tempera ture may rise again and all the symptoms of the disease return In such instances another complete course of the drug will be needed

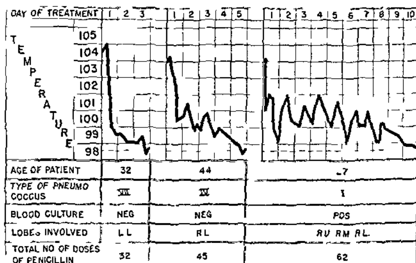


Fig 15 Temperature charts of three patients with pneumococcic pneumonia treated with intramuscular penicillin (15 000 units every three hours)

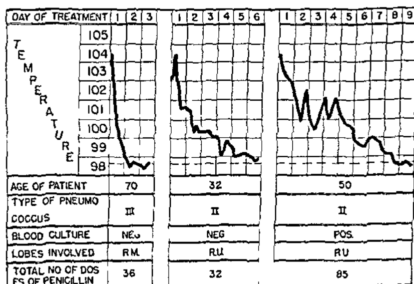


Fig 16 Temperature charts of three patients with pneumococcic pneumonia treated with oral penicillin (75 000 units every three hours)

If the patient does not improve within forty-eight hours if the pneu monia spreads to another lobe or if purulent complications appear the dose of penicillin should be increased Intramuscular doses of 100 000

of the disease or lowers the fatality rate They are accordingly not recommended

Results of Treatment and Prognostic Factors

The prognosis in a given case can be estimated most accurately by considering the effect of certain factors upon the case fatality rate One

TABLE 26

Results of Sulfonamide or Penicillin Treatment of Adult Patients with Pneumococcic Pneumonia According to Age

Age Group	Sulfonamides			Penicillin		
	Number of Cases	Died		Number of Cases	Died	
		Number	Per cent		Number	Per cent
1[illegible]–20	147	4	[illegible] 7	9	0	0
21–30	311	10	3 2	88	0	0
31–40	329	33	10 0	10	3	2 9
41–50	[illegible]08	[illegible]	1[illegible] 0	90	6	6 7
51–60	136	3[illegible]	2[illegible] [illegible]	3	6	17 1
61–70	82	24	29 3	30	5	16
over [illegible]0	37	1	40 5	[illegible]3	5	1
All cases	1 [illegible] 0	148	11 8	400		6 3

of these is the age of the patient (Table 26) Among our patients who were treated with sulfonamides the fatality rate rose for each decade from a low of 2 7 per cent for patients twelve to twenty years of age

TABLE 2[illegible]

Results of Sulfonamide or Penicillin Treatment of Adult Patients with Pneumococcic Pneumonia According to Type of Pneumococcus

Type of Pneumococcus	*Sulfonamides*			*Penicillin*		
	Number of Cases	Died		Number of Cases	Died	
		Number	Per cent		Number	Per cent
I	[illegible]31	18	7 8	57	3	5 3
II	89	3	3 4	34	0	0
III	140	3[illegible]	2 8	4		11 9
IV	76	13	17 1	[illegible]	0	0
V	4[illegible]	1	2 [illegible]	5	0	0
VI	44	4	9 1	15	2	13 3
VII	144	1[illegible]	8 3	47	1	2 1
VIII	68	[illegible]	10 3	[illegible]	2	8 0
Higher types	413	8	14 0	150	12	8 0
All cases	1 [illegible] 0	148	11 8	400		6 3

to a high of 40 5 per cent for patients over seventy With the employment of penicillin the fatality rate was lowered all along the line It was zero in patients from twelve to thirty years of age While it rose progres-

any time We do not believe that therapy which combines penicillin and sulfonamides has any advantage over the employment of penicillin alone

If sulfonamides are preferred to penicillin for any reason sulfadiazine sulfamerazine or sulfathiazole may be started after sputum and blood specimens have been obtained Sulfadiazine should be administered to adult patients in doses of 4 to 6 gm (60 to 90 grains) immediately followed by 1 gm (15 grains) every four hours day and night Children should receive 0 03 gm (½ grain) per pound of body weight as the first dose and 0 06 gm (1 grain) per pound of body weight divided into six doses and administered at four hour intervals Sulfathiazole should be given in the same doses as sulfadiazine Sulfamerazine can be used in

TABLE 25

COMPLICATIONS OBSERVED IN 1250 ADULTS WITH TYPED PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFONAMIDES AND 400 TREATED WITH PENICILLIN

	Treated with Sulfonamides			*Treated with Penicillin*		
	No of Cases	Inci dence (Per cent)	Fatality Rate (Per cent)	No of Cases	Inci dence (Per cent)	Fatality Rate (Per cent)
Delayed resolution	32	2 6	0	19	4 8	0
Pleural effusion	20	1 6	5	3	0 8	0
Empyema	24	1 9	21	3	0 8	33
Relapse	22	1 8	14	5	1 3	0
Lung abscess	10	0 8	40	0		
Meningitis	8	0 6	88	2	0 5	50
Endocarditis	7	0 6	100	0		
Pericarditis	5	0 4	20	1	0 3	100
Otitis media	5	0 4	0	2	0 5	0
Arthritis and/or bursitis	4	0 3	50	1	0 3	0
All bacterial complications	85	6 8	34	14	3 5	21

Excluding delayed resolution and pleural effusion

somewhat smaller doses such as 3 gm (45 grains) initially followed by 1 gm (15 grains) every six hours Sulfonamides should be discontinued according to the rules recommended for penicillin

Specific Antipneumococcus Serums Formerly a specific anti serum was available for pneumococcic pneumonia caused by each of the types from I through XXXIII Its use was followed by a rapid drop in temperature pulse and respiratory rates in most patients Since the advent of the sulfonamides and particularly of penicillin specific serums are falling into disuse

Other Measures of Doubtful Value These include artificial pneumothorax to collapse the affected lobe x ray therapy and diathermy Although advocated at times in the past these methods are rarely used today There is no evidence that any of them favorably affects the course

We[4] have found that in patients treated with sulfonamides who experience a relapse the outcome depends upon the concentration of the drug in the blood at the time when the relapse occurs If the concentration of free sulfonamide is below 2 or 3 mg per 100 cc at the time of the temperature rise vigorous sulfonamide therapy by means of an intravenous dose and an increase in the oral dose thereafter will often cause a prompt recession of fever and toxicity If the relapse occurs in spite of the fact that the concentration has been kept at a high level then the prognosis is bad In such cases penicillin should be given Among the twenty two patients who had a relapse in spite of adequate sulfonamide therapy death occurred in three cases (14 per cent)

We have encountered only five instances of relapse among the 100 patients whom we have treated with penicillin (Table 25) These occurred within a few days after penicillin therapy was discontinued but all the patients recovered promptly when penicillin was given again in the same doses that were used for the original illness

Recurrence is the term used to describe pneumonia developing in a patient who has had a previous attack of the disease from which he has completely recovered The pneumococcus causing the reinfection may belong to the same or to a different type although the shorter the interval between the original and recurrent attacks the greater the likelihood that the same type will cause both attacks The second attack may occur at any site in the lungs irrespective of the location of the original disease[13] When chronic pulmonary disease is present recurrent attacks of pneumonia tend to be more frequent and to occur at shorter intervals than in patients with normal lungs Recurrent attacks should be treated in exactly the same manner as original attacks of pneumonia

Local Complications

The complications which we observed in our patients with pneumococcic pneumonia treated with sulfonamides or with penicillin are listed in Table 25

Delayed Resolution

The time required for removal of the debris within the alveoli and the return of the lung to its normally functioning state after the active pneumonia is over varies from a few days to several months Considering delayed resolution to be present in cases where physical or roentgenographic signs of pulmonary infiltration remained for more than three weeks after the temperature had fallen to normal levels we found that this complication occurred in 2 6 per cent of our patients treated with sulfonamides and in 4 8 per cent of our patients treated with penicillin The occurrence of delayed resolution has no relation to the severity of the original illness or to the type of therapy employed It is encountered in a higher percentage of persons in the older age groups During the

sively as the patient's ages increased, it was lower in each age group than the corresponding fatality rate for the sulfonamide treated patients.

The type of the infecting pneumococcus is also a prognostic factor. Pneumonias caused by the Type III pneumococcus have always been accompanied by a high case fatality rate. This is true in our series (Table 27). Among the patients with this type of pneumonia who were treated with sulfonamides 22.8 per cent died. Although the fatality rate was reduced to 11.9 per cent among the penicillin treated patients this is still high in comparison with the fatality rate of 6.3 per cent for the entire group of patients who received penicillin.

It has long been known that the prognosis is worse when the pneumococci can be cultured from the blood stream. Table 28 shows that the case fatality rate was about three times as high among our patients with bacteremia as among the nonbacteremic patients, whether the patients were treated with sulfonamides or with penicillin. The fatality rate was lower, however, for the patients treated with penicillin, both among those with positive and those with negative blood cultures.

TABLE 28

RESULTS OF SULFONAMIDE OR PENICILLIN TREATMENT OF ADULT PATIENTS WITH PNEUMOCOCCIC PNEUMONIA ACCORDING TO PRESENCE OF PNEUMOCOCCI IN THE BLOOD

	Sulfonamides			*Penicillin*		
	Number of Cases	Died		Number of Cases	Died	
		Number	Per cent		Number	Per cent
With positive blood culture	191	48	25.1	43	7	16.3
Without positive blood culture	1059	100	9.4	357	18	5.0
All cases	1250	148	11.8	400	25	6.3

RELAPSE AND RECURRENCE

Relapse of a pneumonia means an exacerbation of the disease in a patient who is apparently improving. It may be caused by the same organism, by a different type of pneumococcus, or by another causative agent such as the hemolytic streptococcus or the Klebsiella (Friedlander) bacillus. The evidences of this phenomenon are usually a sudden rise in temperature and increase in toxicity, sometimes accompanied by pleural pain, and the reappearance of pink or rusty sputum. Although the fresh infection may be in the same lobe, more often the relapse denotes a spread of the pneumonia to a lobe adjacent to the original one or to a site in the opposite lung. When the latter occurs it is considered to be caused by coughing of the sputum into the trachea and aspirating it into the bronchi of the opposite lung.

Symptoms and Signs In occasional cases the temperature drops to normal or nearly normal levels as a result of serum sulfonamide or penicillin treatment only to rise again after a day or two More commonly the temperature does not fall to any extent but continues to reach a daily peak which may vary in individual cases anywhere from 100 to 105° F with remissions each day of 2 or 3 degrees The pulse rate is correspondingly accelerated When a large amount of fluid is present the patient may be quite dyspneic If the condition continues without any treatment for some time the patient becomes weak exhausted and emaciated

Physical examination of the chest reveals the typical signs of fluid or less often the signs of consolidation with distant breath sounds and voice sounds

Laboratory and Special Examinations One important differential point is that the total leukocyte count and the percentage of granulocytes remain above normal limits Roentgenograms and fluoroscopy help in diagnosing an effusion but chief reliance should be placed on aspirated fluid Usually the fluid is in the lower part of either pleural cavity rarely in both Sometimes it is interlobar and sometimes pocketed elsewhere When effusion is suspected in other places a needle should be inserted directly over the area When fluid is in the base of a lung aspiration is best attempted in the seventh intercostal space near the angle of the scapula Fluid removed from the chest of a patient with pneumonia should always be cultured even though it looks clear A smear stained by the gram method and a leukocyte count should also be done Sometimes organisms are seen on smear but are not found on culture or no organisms may be detected by either means and yet many leukocytes may be present Such effusions are classified as empyemas since the only living organisms may be in the pleura while those in the fluid may all be dead

Treatment Although we have seen empyemas disappear in rare instances under sulfonamide therapy alone in the majority of cases sulfonamides have no effect upon the pleural infection once it has begun Some observers even feel that the continued use of these drugs after empyema has developed causes more loculation of the fluid than would otherwise occur and thus makes surgical drainage more difficult

The use of penicillin on the other hand has resulted in complete recovery in many cases without the necessity of surgical treatment [3, 15] At the present time there is considerable controversy regarding the proportion of empyema patients who ultimately require surgical drainage It is our opinion that if patients with pneumococcic empyema are treated early in the course of the disease with adequate amounts of penicillin for sufficiently long periods of time from 50 to 75 per cent of them will be cured by this procedure alone The presence of other organisms (especially those which produce a putrid empyema or are insensitive to penic

course of resolution sputum may plug a small bronchus or bronchiole giving rise to atelectasis. This phenomenon serves to delay resolution in many patients.

McGibbon[9] has stressed the fact that so-called unresolved pneumonia may actually be due to some other intrathoracic lesion. He recommends that bronchoscopy be performed if roentgenograms do not show any improvement. It is also advisable to examine the sputum of such patients for tubercle bacilli since we have seen several patients with lower lobe tuberculosis who were erroneously thought to have an unresolved pneumonia.

There is no treatment which has been proved to hasten resolution although it has been claimed that x-ray therapy will accelerate the process. Occasionally fibrosis may supervene so that complete clearing never occurs.

Pleurisy with Effusion

The pleura is affected in nearly every case of pneumonia and undoubtedly a small amount of fluid exudes into the pleural space in all such cases. Large amounts of fluid were found in 1.6 per cent of our patients who received sulfonamides and in 0.8 per cent of those who received penicillin (Table 25). Inasmuch as a degree or two of fever often accompanies a sterile pleural effusion, it is important to differentiate this condition from empyema. This can only be done by withdrawing some fluid and culturing it. If the fluid proves to be sterile it should be left alone and allowed to reabsorb unless embarrassment of respiration requires its removal.

We do not subscribe to the opinion held by some clinicians that penicillin should be injected intrapleurally as a prophylactic against infection when the pleural fluid is sterile. If empyema is actually developing in such fluid, one injection of penicillin is not likely to sterilize the area. Instead it will merely suppress the infection for a while and thus delay the ultimate diagnosis and treatment.

Empyema

The pathological condition in which bacteria can be cultured from the pleural fluid is called empyema or more properly *empyema thoracis*. Before the advent of the sulfonamides about 5 per cent of patients with pneumococcic pneumonia developed empyema. Chemotherapy has produced a remarkable decrease in the incidence of this complication. It was observed in 1.9 per cent and 0.8 per cent of our patients treated with sulfonamides and with penicillin respectively (Table 25). Empyema is more likely to occur in the most severely ill patients and in those with bacteremia, although other patients are by no means exempt. It is especially common when the pneumonia is caused by type I or type V pneumococci.

Symptoms and Signs In occasional cases the temperature drops to normal or nearly normal levels as a result of serum sulfonamide or penicillin treatment only to rise again after a day or two More commonly the temperature does not fall to any extent but continues to reach a daily peak which may vary in individual cases anywhere from 100° to 105° F with remissions each day of 2 or 3 degrees The pulse *rate is correspondingly accelerated When a large amount of fluid is* present the patient may be quite dyspneic If the condition continues without any *treatment for some time* the patient becomes weak exhausted and emaciated

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There is no treatment which has been proved to hasten resolution although it has been claimed that x ray therapy will accelerate the process Occasionally fibrosis may supervene so that complete clearing never occurs

Pleurisy with Effusion

The pleura is affected in nearly every case of pneumonia and undoubtedly a small amount of fluid exudes into the pleural space in all such cases Large amounts of fluid were found in 1 6 per cent of our patients who received sulfonamides and in 0 8 per cent of those who received penicillin (Table 25) Inasmuch as a degree or two of fever often accompanies a sterile pleural effusion it is important to differentiate this condition from empyema This can only be done by withdrawing some fluid and culturing it If the fluid proves to be sterile it should be left alone and allowed to reabsorb unless embarrassment of respiration requires its removal

We do not subscribe to the opinion held by some clinicians that penicillin should be injected intrapleurally as a prophylactic against infection when the pleural fluid is sterile If empyema is actually developing in such fluid one injection of penicillin is not likely to sterilize the area Instead it will merely suppress the infection for a while and thus delay the ultimate diagnosis and treatment

Empyema

The pathological condition in which bacteria can be cultured from the pleural fluid is called empyema or more properly *empyema thoracis* Before the advent of the sulfonamides about 5 per cent of patients with pneumococcic pneumonia developed empyema Chemotherapy has produced a remarkable decrease in the incidence of this complication It was observed in 1 9 per cent and 0 8 per cent of our patients treated with sulfonamides and with penicillin respectively (Table 25) Empyema is more likely to occur in the most severely ill patients and in those with bacteremia although other patients are by no means exempt It is especially common when the pneumonia is caused by type I or type V pneumococci

LUNG ABSCESS

Solitary lung abscess is an infrequent complication having been observed in 0 8 per cent of our patients treated with sulfonamides (Table 25) This is approximately the same incidence as was reported before the sulfonamide era None of our 100 patients who received penicillin have developed a lung abscess Usually the temperature and leukocyte count continue moderately elevated and infiltration remains in the affected areas where it is accompanied by many large moist rales The sputum increases in amount and sooner or later the roentgenograms show the presence of cavities Although occasional cases of lung abscess heal on bed rest and postural drainage alone the majority must be drained surgically Some surgeons prefer to do this immediately after the diagnosis is made but the consensus at present is that one may wait for spontaneous recovery no longer than three weeks after the onset of the abscess In competent hands drainage nearly always results in recovery

Complications of Pneumococcic Pneumonia and Diseases Caused by the Pneumococcus in Other Organs

PERICARDITIS

This complication was present in 1 to 2 per cent of patients with pneumonia before sulfonamides were used We have found it in 0 4 and 0 3 per cent of the patients treated with sulfonamides and penicillin respectively (Table 25) It may follow extension of a neighboring empyema or it may be blood borne A friction rub synchronous with the heart beat should make the clinician suspect this complication although the same phenomenon may occur when there is a dry pleurisy near enough to the heart so that the pleural layers will rub together with each heart beat Uremia must also be ruled out as the cause of a pericardial friction rub Fluoroscopy and roentgenograms are of the greatest value in the diagnosis A diagnostic pericardial tap may be tried but the advantages to be gained should be weighed against the not inconsiderable risk An effusion large enough to cause cardiac tamponade must be removed Surgical drainage may be necessary in spite of the risk which attends it

ENDOCARDITIS

Pneumococcic endocarditis is an infrequent complication having been found in 0 3 to 3 per cent of patients with pneumococcic pneumonia treated without sulfonamides It was present in 0 5 per cent of our sulfonamide treated patients and in none of those who received penicillin (Table 25) Endocarditis may begin during any stage of the pneumonia or may even appear after a seemingly normal convalescence In about one fourth of the cases it develops from a condition other than a pneumonia such as mastoiditis or meningitis Patients in middle and late life are usually affected

illin) or the presence of thick pus of multiple pockets of infection of a thickened pleura or of bronchopleural fistula is responsible for many of the failures of penicillin treatment although even these patients will sometimes get well with the use of penicillin alone

We recommend the following procedure As much fluid as can be removed conveniently and without embarrassment of respiration should be aspirated If the fluid is thick or contains large pieces of fibrin isotonic salt solution may be injected into the pleural cavity and removed along with the fluid After this 200 000 units of penicillin dissolved in a volume of isotonic salt solution which equals about one fourth to one half of the amount of fluid removed should be injected through the same needle This procedure should be repeated every twenty four hours or if the patient is very toxic every twelve hours until definite improvement is manifest Then the injections may be spaced at forty eight hour intervals

In favorable cases the organisms disappear from the stained smear and can no longer be cultured after the first one to three injections Soon after the first injection there is almost always a drop in the temperature and a pronounced diminution in the patient s toxicity These are no doubt due partly to the removal of a large quantity of pus but are also partly an early effect from the penicillin itself The temperature reaches normal or nearly normal levels within a few days and in favorable cases remains or becomes entirely normal within three or four weeks at the most A fall in the pulse rate follows several days behind the initial drop in temperature The leukocyte count descends progressively and the patient regains his appetite and with it his weight and strength The pleural fluid although it gets thicker for a while later becomes serous again When these results have been obtained and the temperature has been practically normal for a week or more the intrapleural injections may be discontinued If fever toxicity and leukocytosis return and above all if the organisms reappear penicillin therapy should be started again and kept up for a longer period of time Adjuvant systemic penicillin therapy is not necessary unless there are other foci of infection present such as pneumonia arthritis meningitis and so forth

If positive cultures persist if the favorable clinical symptoms described above do not appear within two or three weeks or if the patient becomes worse in spite of the penicillin treatment it is best to resort to surgical drainage This usually consist in the resection of one or more ribs and the insertion of a tube

If the empyema is found to be pocketed in two or more areas attempts may be made to aspirate pus from and inject penicillin into each of these If this is not successful surgical drainage will be required The indications for surgical treatment in patients receiving penicillin have been discussed by Blades [1]

As shown in Table 25 it was noted in 0 7 per cent of our patients treated with these drugs and in 0 5 per cent of those treated with penicillin

Pneumococcic meningitis may occur following conditions other than pneumonia Table 29 shows the source of infection in fifty five cases observed by us

When symptoms or signs of meningitis are present in conjunction with pneumonia the pneumococcus is the most likely cause The diagnosis can be made with certainty only by examination of the cerebrospinal fluid This should be done in every patient with pneumonia who is stuporous or comatose who exhibits continued delirium or who has neurologic signs suggestive of meningitis

The cerebrospinal fluid should be examined according to the directions on page 208 When meningitis is present this fluid usually contains from

TABLE 29

OUTCOME OF PNEUMOCOCCIC MENINGITIS IN RELATION TO THE PRIMARY SOURCE OF INFECTION

Source of Infection	*Number Treated*	*Died*	
		Number	Per cent
Pneumonia	21	14	67
Otitis media and/or mastoiditis	10	2	20
Endocarditis	2	2	100
Head injury (fractured skull)	1	0	
Primary focus not known (history unobtainable)	11	11	100
No primary focus found	10	3	30
Total	5	32	58

100 to 5000 cells per cu mm most or all of which are granulocytes In most cases the dextrose content is decreased or absent and the protein increased The pneumococci are often seen on direct smear of the centrifuged sediment and may be typed directly by the capsular swelling method When this is not successful the organisms are almost invariably obtained by culture

Prognosis Only an occasional patient recovered from pneumococcic meningitis in the presulfonamide days With the use of the sulfonamides the prognosis has improved although we[14] have observed only three (8 per cent) recoveries among forty patients treated with full doses of sulfonamides in conjunction with specific serum Among fifty five patients whom we treated with penicillin in conjunction with sulfonamides thirty two (58 per cent) recovered (Table 30) The best results were obtained in patients in whom there was no discernible primary focus of infection or in whom the disease followed otitis media or a head injury The poorest results occurred in patients in whom meningitis developed following pneumonia and in those with an associated endocarditis Age is an important factor in recovery The best results are obtained in patients in the second third and fourth decades

The vegetation may be on a previously damaged valve although in most instances a preexisting lesion is not present Tinsley[17] found that the following valves were affected in ninety collected cases

Aortic	3[illegible] cases
Mitral	30 cases
Tricuspid	11 cases
Aortic and mitral	7 cases
Aortic and tricuspid	6 cases
Mitral aortic and tricuspid	1 case
Mitral tricuspid and pulmonic	1 case
Mitral aortic tricuspid and pulmonic	2 cases

In rare instances vegetations may be present on the endocardium without involving the valves and occasionally pneumococcic endarteritis of a patent ductus arteriosus has been observed

Symptoms and Signs The temperature is usually elevated to a daily peak between 103° or 105° F and may be continuous or remittent Frequent chills are often present Murmurs indicative of valvular lesions appear When aortic lesions are present a fall in the diastolic blood pressure with consequent increase in the pulse pressure may be the first clew to the presence of a valvular lesion Petechiae are present in less than half of the cases Purulent foci elsewhere in the body often occur Arthritis and pericarditis are among these while meningitis is especially common When pneumonia is not the primary lesion it may appear during the course of the endocarditis as a result of pulmonary infarction

Diagnosis The diagnosis rests upon repeatedly positive blood cultures in a patient with pneumonia in whom signs of endocarditis also appear A positive blood culture coincidental with agglutinins against the identical type of pneumococcus is practically pathognomonic

Prognosis Only a rare patient with pneumococcic endocarditis ever recovered with the use of antipneumococcic serum or sulfonamides Most patients in the pre penicillin era died within a month of the onset

Treatment Since penicillin has been available several cases have been reported in which recovery has occurred although this type of therapy has not been invariably successful It is important that the condition be recognized early before destruction of the valves has taken place and that large doses of penicillin be given The regimen of treatment given in the section on *Streptococcus viridans* endocarditis (p 178) should be followed

Meningitis

Meningismus occurs occasionally during the course of pneumonia in adults and in about 10 per cent of children This symptom is of no consequence and does not necessarily mean that a meningitis will occur later True purulent meningitis occurred in 1 to 2 per cent of patients with pneumococcic pneumonia before the advent of the sulfonamides

possible in doses of 1 gm (15 grains) every four hours for adults or 0 06 to 0 1 gm (1 to 1½ grains) for each twenty four hour period divided into six four hourly doses If it is necessary to give these drugs parenterally one-sixth of the twenty four hour dose should be given subcutaneously as the sodium salt in a 1 per cent solution every six hours Close check upon the concentration of the drug in the blood is required when parenteral administration is employed

Arthritis

The pneumococcus may cause a purulent arthritis as an infrequent complication of pneumonia and more rarely following some other focal pneumococcic infection or without any antecedent infection In older series arthritis was reported in from 0 1 to 0 6 per cent of cases of pneumococcic pneumonia We have seen it in 0 3 per cent of our patients whether treated with sulfonamides or with penicillin

This condition usually attacks only one joint sometimes two The knee and the ankle are most frequently involved Clinically the disease resembles other purulent arthritides with heat and swelling of the joint the latter often to a considerable degree Sometimes there is an associated bursitis while occasionally this complication may occur independently of arthritis

Arthritis caused by the pneumococcus must be differentiated from the arthropathy which occurs during serum sickness and the arthralgias which occasionally occur as a manifestation of sensitivity to the sulfonamides or penicillin Furthermore rheumatoid or other types of arthritis may occur during the course of pneumonia as well as at any other time Primary pneumococcic arthritis must be differentiated from other kinds of purulent arthritis In any case the diagnosis depends upon aspiration and bacteriological examination of the fluid in the joint Whether the disease was primary or followed another pneumococcic infection treatment by means of general administration of the sulfonamides and repeated aspirations was often successful [2] Sometimes incision and often drainage were necessary Since the introduction of penicillin the treatment of choice is the intra articular injection of 50 000 units of this antibiotic on alternate days until local and general signs of inflammation have disappeared If infection is present elsewhere in the body penicillin should be given systemically in addition in the same doses as for pneumonia or in higher doses

Otitis Media and Mastoiditis

Otitis media is a frequent complication of pneumonia and was present in 12 to 40 per cent of children and 1 to 3 per cent of adults with pneumonia before the advent of the sulfonamides Since that time the incidence in children has apparently been reduced although definite figures are not available As shown in Table 25 we have encountered otitis

Waring[18] found that among sixty children treated with sulfonamides with or without specific serum in addition 22 per cent of those under two years of age recovered as compared with 64 per cent of those over two years of age. Among twelve patients (mostly children) treated with penicillin and sulfonamides only one died. Thus it is apparent that the prognosis is best in the age groups between two and forty years and that at all ages the results are better when penicillin is used in addition to sulfonamides.

It has been our experience that patients do poorly when many pneumococci (more than four per high power field) are present in the centrifuged sediment from the initial specimen of spinal fluid.

Treatment. 1. As soon as the diagnosis has been established 20 000 units of penicillin dissolved in 10 cc or less of isotonic salt solution should be injected intrathecally at a slow rate after the removal of a slightly greater quantity of spinal fluid. This should be followed by 20 000 units each day. In infants these doses may be halved.

TABLE 30

OUTCOME OF PNEUMOCOCCIC MENINGITIS IN RELATION TO THE AGE OF THE PATIENT

Age	*Number Treated*	*Died*	
		Number	Per cent
0–9	5	2	40
10–39	8	2	25
40 and over	42	28	67
Total	55	32	58

If signs of subarachnoid block develop, it may be necessary to inject the penicillin into the lateral ventricles or into the cisterna magna. In our experience the former route is to be preferred as cisternal injections are attended by considerable hazard.

2. Penicillin should also be given systemically in doses of 500 000 to one million units for each twenty-four hour period, administered either by continuous intramuscular or intravenous infusion or by intramuscular injections at intervals of two hours.

Recovery should be judged by a drop in the temperature and pulse rate, by the disappearance of signs of meningitis, especially by the patient's progress in reorientation, by the disappearance of organisms from smear and culture and the return of the dextrose values to normal levels. Treatment should not be discontinued until these manifestations have been normal for one week.

3. Sulfonamides should be given in an initial intravenous dose of 6 gm (90 grains) of sodium sulfadiazine or sodium sulfamerazine in adults and 0.03 to 0.05 gm (½ to ¾ grain) per pound of body weight in children. Maintenance doses should be given orally or by stomach tube where

or hematuria occurs sulfonamides should be discontinued until the physician is sure that they are not the cause of the trouble

Rarer complications of pneumococcic pneumonia include hemorrhage from the stomach or the intestines abscesses of the skin peripheral neuritis pyelitis parotitis orchitis and thrombosis of the veins of the legs and thighs

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media in only 0 3 per cent of sulfonamide treated and 0 5 per cent of penicillin treated adults with pneumonia

Otitis media is often present before the onset of the pneumonia When it first occurs during the disease it may not be recognized In children with pneumonia it is important that the ears be examined daily while in an adult patient any complaint of pain in the region of the ears should be investigated The disease may extend into the mastoid cells and from there into the meninges

Under sulfonamide and particularly under penicillin treatment the condition often clears up without surgery The treatment of choice at the present time is penicillin in doses of 15 000 units every three hours or 300 000 units of penicillin in beeswax and oil every twelve hours by intramuscular injection or 75 000 to 100 000 units orally every three hours Surgical drainage should be employed promptly when the infection does not respond to sulfonamides and penicillin

Sinusitis

Inflammation of the paranasal sinuses is present in an undetermined number of cases of pneumonia Pneumococci of the same type as those found in the sputum have been demonstrated in the infected sinuses In the absence of pneumonia sinusitis is seldom caused by pneumococci The main significance of sinusitis is that it may act as a pathway of infection to the meninges

Peritonitis

Inflammation of the peritoneum is a rare complication of pneumonia in children and is rare indeed in adults It is more frequently primary than secondary to pneumonia The primary form occurs in children especially as a complication of nephrosis and in girls as an extension of vulvovaginitis It responds favorably to treatment with sulfonamides or penicillin

Other Complications

Conjunctivitis is also a rare complication of pneumonia It occurs more often as a primary disease in which instance it responds well to local treatment with sulfonamides or penicillin

Acute nephritis occurs occasionally during the course of or convalescence from pneumococcic pneumonia Whether it is ever due to the pneumococcus or whether it is dependent upon infection by the *Streptococcus hemolyticus* is a disputed question Certainly it follows pneumococcic pneumonia far less frequently than it follows diseases caused by the hemolytic streptococcus Crystals and calculi formed from the sulfonamide drugs cause a picture which may be confused with that of acute nephritis but their presence is not associated with casts or changes in the blood pressure Whenever pain in the region of the kidneys oliguria

cause a streptococcic sore throat in one patient streptococcic sore throat with rash (scarlet fever) in another and otitis media pneumonia puerperal sepsis or erysipelas in still other patients Almost all the types which cause infections in humans belong to Group A Hemolytic streptococci belonging to Groups B C and C are responsible for a few human infections while streptococci of the other groups cause disease in man only rarely

Hemolytic streptococci are usually introduced into the human body by way of the upper respiratory tract causing disease especially in the

TABLE 31

SITE OF INFECTIONS CAUSED BY HEMOLYTIC STREPTOCOCCI IN RELATION TO THE PATIENT S AGE

Site of Infection	*Disease*	*Age Group Particularly Affected*
A Upper respiratory tract	(1) Childhood type of streptococcic fever	Under 3 years
	(2) Sore throat with rash (scarlet fever)	3 to 10 years
	(3) Sore throat without rash	Over 10 years
	(4) Nasopharyngeal carriers	All ages
B Associated with upper respiratory tract	(1) Otitis media mastoiditis (2) Sinusitis (3) Peritonsillar and retropharyngeal abscess (4) Cervical adenitis	All ages especially under 14 years
C Skin and associated areas	(1) Erysipelas (2) Pyoderma (3) Cellulitis	Under 5 years and over 40 years
D Other sites (usually by extension or metastasis from Groups A B and C)	(1) Vaginitis	Under 10 years
	(2) Puerperal sepsis	In child bearing ages
	(3) Lymphadenitis (4) Bacteremia (5) Meningitis (6) Purulent arthritis (7) Osteomyelitis (8) Peritonitis (9) Pneumonia	All ages especially under 14 years

pharynx or in areas adjacent to or connected with it (Table 31 *A* and *B*) The less common avenue of infection is by way of contaminated hands or objects to the skin itself (usually where it has already been abraded) or to adjacent areas For instance the organisms may be introduced into the openings of the breast glands causing mastitis or into the vagina with resulting vaginitis or puerperal sepsis (Table 31 *C*) Sometimes the streptococci advance beyond the area of primary invasion and reach other organs of the body (Table 31 *D*)

It is also evident from Table 31 that the kind of disease which results

8 Streptococcic Infections

Infections with Beta Hemolytic Streptococci

Introduction

The streptococci are gram positive cocci which grow characteristically in chains The most widely used classification is based upon the appearance of the colonies on a blood agar plate When the individual colonies are surrounded by a zone of greenish discoloration the organism is called an alpha streptococcus or *Streptococcus viridans* When there is a clear zone around each colony the organism is a beta hemolytic streptococcus or *Streptococcus haemolyticus* If there is neither a greenish zone nor a clear zone the organism is called a gamma streptococcus or *Streptococcus nonhaemolyticus* The beta hemolytic streptococci can be separated into groups A through N based on precipitin reactions performed by the Lancefield[15] technique Group A streptococci are further divided into forty six serological types by the anti M precipitin method of Lancefield or the agglutination method of Griffith[7]

This bacteriologic classification of the streptococci is important for two reasons First the streptococci which are pathogenic for man are usually beta hemolytic and most of them fall within Group A Secondly when nonhemolytic streptococcus infections (i e those caused by alpha and gamma streptococci) occur in humans they differ widely from those caused by beta hemolytic streptococci The latter act rapidly invade tissues extensively and produce a number of toxins As a result beta hemolytic streptococcus infections have a short incubation period a sudden often overwhelming onset frequently cause profound toxemia and may be fatal within a few hours or days

Infections caused by nonhemolytic streptococci on the other hand seldom invade normal tissues They seem inclined to engraft themselves and to multiply only upon physiologically or anatomically altered organs Even then the disease is often mild and its progress slow unless hastened by other factors

Infections with Beta-Hemolytic Streptococci

With the multiplicity of groups and types of beta hemolytic streptococci one might expect a particular type to cause a specific disease but this is not so Any one of several different types may cause one of the streptococcic diseases likewise an individual type of streptococcus may

Susceptibility to this toxin can be measured by injecting a known amount of the toxin intradermally (the Dick test for details see page 115) In general if the individual has a positive Dick test (is susceptible to the toxin) before he becomes infected with hemolytic streptococci which produce the erythrogenic toxin he will develop scarlet fever whereas if he has a negative Dick test (is not susceptible to the toxin) he will suffer from the local manifestations of the streptococcic infection only without the accompanying rash of scarlet fever Accordingly we have chosen to discuss streptococcic sore throat as an entity including the rash of scarlet fever as an incidental circumstance

Clinical Characteristics of Streptococcic Sore Throat

Symptoms and Signs The onset is usually sudden with chilly sensations or chills fever headache malaise and in the severe cases prostration Vomiting may be present from the start especially in children Pharyngeal symptoms vary from a slight soreness all the way to constant pain so severe that the patient feels that it will be impossible to take the next swallow

In a severe case the posterior pharyngeal wall is fiery red and edematous and presents a glistening glairy appearance in its entire extent except when there are grayish white patches of exudate The exudate resembles that seen in diphtheria but it is easily wiped off and does not leave a bleeding surface The uvula is red and frequently edematous The anterior pillars are injected The tonsils when present are invariably enlarged and are usually covered with patches of exudate In milder cases the injection of the membranes will be less intense and there will be little or no exudate and no edema Unless the rash of scarlet fever is present these cases will often be indistinguishable clinically from cases of nonspecific pharyngitis

Course The temperature may be only slightly elevated or may be as high as 105 F In the average case its maximum is 102 to 103 F It remains at this level anywhere from twenty four hours to five days unless specific treatment is given and usually subsides by lysis

Clinical Characteristics of Scarlet Fever
(Streptococcic Sore Throat with Rash)

Symptoms and Signs These are the same as in streptococcic sore throat without rash except that vomiting is more frequent in scarlet fever and a higher proportion of the patients may show evidences of general toxicity

The rash produced by the erythrogenic toxin appears within two to three hours of the initial symptoms or may be delayed up to twenty four hours The rash comprises an erythematous blush as a background on top of which are tiny punctate spots uniformly spread and close

from infection with hemolytic streptococci depends upon the age of the patient[19] In children under three years of age infection of the upper respiratory tract usually takes the form of a mild rhinopharyngitis (Table 31 A) in children between the ages of three and ten years the same organism localizing in the same place is likely to produce a more severe infection of the throat accompanied by a toxic rash (scarlet fever) After the age of ten years most individuals have acquired immunity to the toxin causing the rash so that they are likely to develop the acute pharyngitis without the rash The areas which are invaded directly from the upper respiratory tract can be affected at all ages although they are more frequently involved in children since upper respiratory infections with hemolytic streptococci are in general more frequent in this age group

Because the skin s powers of resistance are at their lowest in very young and very old patients infections of the skin are found especially in these age groups Puerperal sepsis of course is found in women of the child bearing ages Involvement of other parts of the body can occur in patients of all ages although the meninges bones and joints are especially likely to be affected in childhood

Childhood Type of Streptococcic Fever

In children under the age of six months hemolytic streptococci often cause a mild nasopharyngitis[19] with irregular low grade fever a serous or mucoid nasal discharge and perhaps some vomiting and diarrhea The acute disease seldom lasts more than a week Sometimes it is attended by even milder symptoms In children between six months and three years of age the infection is likely to be more severe After an initial short period of nasal discharge the pharynx will become diffusely red and soon afterward the cervical lymph nodes will swell and become tender Irregular fever up to 103 F and occasionally higher anorexia and vomiting will be present during the height of the local inflammation Complications such as otitis media or suppurative lymphadenitis may develop The course extends over ten days to six weeks and convalescence is often prolonged A definite diagnosis can usually be made only by culturing group A hemolytic streptococci from the nose or throat Treatment which is the same as for streptococcic sore throat in older patients is outlined on page 148

Streptococcic Sore Throat (Septic Sore Throat) Including Scarlet Fever

Hemolytic streptococci produce several toxins one of which is called the erythrogenic toxin When these organisms multiply within the body (usually in the pharynx) of a susceptible individual so as to liberate a sufficient amount of this toxin or if this quantity of toxin is injected into a nonimmune subject such a person will develop the characteristic rash of scarlet fever together with general symptoms of toxicity

the form of small flakes less often in large sheets or in the shape of casts of a finger toe hand or foot

An enanthem usually occurs in scarlet fever in the form of small bright red hemorrhagic spots on the soft palate and anterior pillars Its *onset may precede or follow that of the skin rash by a day or two*

The tongue at first is usually heavily coated with a thick cream colored fur After this its appearance is characteristic of scarlet fever The papillae swell and push their way through to appear as scattered *bright red knobs—the so called strawberry tongue Later the coating* peels beginning at the tip and edges then over the anterior half of the dorsum and finally the entire tongue leaving a surface which looks like raw beef After several more days the normal coating returns so that by the third week the tongue has resumed its usual appearance

Clinical Types Scarlet fever may be divided into four types according to the severity of the various manifestations as shown in Table 32

1 The mild type In this form of the disease the onset is usually indefinite the temperature remains below 101 F the rash is often slight and evanescent involvement of the pharynx is minimal complications are infrequent and recovery often begins within twenty four to forty eight hours

2 The moderately severe type Here the onset is usually abrupt and is accompanied by vomiting the maximum temperature ranges between 101 and 103 F the rash is usually extensive and bright red and redness is present all over the pharynx and is often accompanied by edema Complications occur frequently although they are seldom severe and defervescence usually begins on the second to the fifth day

3 The toxic or fulminating type Symptoms of general toxicity are great in this type in proportion to the amount of pharyngeal involvement The onset is rapid vomiting persistent headache intense and prostration severe The rash may be a bright red or it may take on a dusky mottled purplish hue due to associated peripheral circulatory failure Sometimes the rash is hemorrhagic in character Hemorrhages in the mucous membranes may result in epistaxis hematemesis and hematuria Death may occur within a few hours or a few days

4 The septic type This is characterized by extensive involvement of the pharynx and nearby structures The cervical lymph nodes are swollen and the surrounding tissues edematous There is a considerable degree of edema and exudate in the throat along with evidences of paranasal sinusitis Otitis media is common Abscesses around the tonsils behind the pharynx or in the neck may occur The temperature remains high and other symptoms of general toxicity are present The rash on the other hand may be no more marked than in moderately severe cases The prognosis in the septic type depends upon the extension of the local process and the severity of the complications It must be emphasized

together so as to give an appearance of bright uniform redness In the Negro the erythema may not be evident Instead the skin may give the appearance of goose pimples with a blackening of the tips The eruption begins on the upper part of the trunk and extends upward onto the neck and down over the extremities Usually there is no eruption on the face or scalp but the cheeks are flushed leaving a relatively light area around the mouth known as *circumoral pallor* Herpes often appears on the lips The rash is accentuated in the axillae groins and popliteal spaces The



(Fig 17 Early eruption of scarlet fever (Courtesy of Parke Davis and Company)

folds of the skin in these areas take on a deeper red color which does not fade on compression These are called Pastia s lines Slight rashes may fade within twenty four hours the more intense ones usually begin to disappear within two to five days

At some time between the fifth day and the fifth week the skin begins to peel in the areas where the rash was present Peeling begins most often on the tips of the fingers or toes under the distal end of the nail but may begin elsewhere on the neck chest or back Peeling may be in

the form of small flakes less often in large sheets or in the shape of casts of a finger toe hand or foot

An enanthem usually occurs in scarlet fever in the form of small bright red hemorrhagic spots on the soft palate and anterior pillars Its onset may precede or follow that of the skin rash by a day or two

The tongue at first is usually heavily coated with a thick cream colored fur After this its appearance is characteristic of scarlet fever The papillae swell and push their way *through to appear as scattered* bright red knobs—the so-called strawberry tongue Later the coating peels beginning at the tip and edges then over the anterior half of the dorsum and finally the entire tongue leaving a surface which looks like raw beef After several more days the normal coating returns so that by the third week the tongue has resumed its usual appearance

Clinical Types Scarlet fever may be divided into four types according to the severity of the various manifestations as shown in Table 32

1 *The mild type In this form of the disease the onset is usually* indefinite the temperature remains below 101 F the rash is often slight and evanescent involvement of the pharynx is minimal complications are infrequent and recovery often begins within twenty four to forty-eight hours

2 The moderately severe type Here the onset is usually abrupt and is accompanied by vomiting the maximum temperature ranges between 101 and 103 F the rash is usually extensive and bright red and redness is present all over the pharynx and is often accompanied by edema *Complications occur frequently although they are seldom severe and* defervescence usually begins on the second to the fifth day

3 The toxic or fulminating type Symptoms of general toxicity are great in this type in proportion to the amount of pharyngeal involvement The onset is rapid vomiting persistent headache intense and prostration severe The rash may be a bright red or it may take on a dusky mottled purplish hue due to associated peripheral circulatory failure Sometimes the rash is hemorrhagic in character Hemorrhages in the mucous membranes may result in epistaxis hematemesis and hematuria Death *may occur within a few hours or a few days*

4 The septic type This is characterized by extensive involvement of the pharynx and nearby structures The cervical lymph nodes are swollen and the surrounding tissues edematous There is a considerable degree of edema and exudate in the throat along with evidences of paranasal sinusitis Otitis media is common Abscesses around the tonsils behind the pharynx or in the neck may occur The temperature remains high and other symptoms of general toxicity are present The rash on the other hand may be no more marked than in moderately severe cases The prognosis in the septic type depends upon the extension of the local process and the severity of the complications It must be emphasized

TABLE 32

T es o Scarle Fe e and Th Tre m nt

Cl cal Type	De r ption f Type				T eatment			
	F pe tu	R t	C F tality R t	Co pl cat ons	Pt ryn T ns ls U ls	I ll n	Se um	
							Con alescent Serum	Scarl t F v Ant tox n
M ll	Bel w 101 F	Sl gl t o mod at ly t ns	Ap 1%	I f eq t	Sl gl tly l ed	Employn nt pt o al, b t ho ld be g n f compl cat ons p e nt	Not eed d	
Mod t ly s	101 F to 103 8 F	F te	to %	Freq t	Mod rat l e- n t	All cases	Not n eded nl ss no imp ovem t fr m pen cill	
							0 to 40 cc intr ously	9000 to 18 000 units nt a en u ly o i t n sc l ly
Se e ( ) t (f lm t g)	104 F d abo	B gl t ed m ttled p pl al red	10 to 15%	M y o m y n t l p ese t	V es—oft l ght	All c ses	Not needed l ss no imp ovem t f om pe ll n o u less p t t s tr m ly ll wl e first see	
							40 to 100 cc intr eno ly	18 000 to 36 000 units i t a en ously ntr musc l ly
(b) Sept t	U lly 104 F abo	V s—ofte al ght	10 to 15%	M y nd se	M ked ol m t	All cases	N t need l u l ss no mpro m nt of g al to c ty wh n pen ll n ployed	
							0 to 100 cc i tr v no ly	9000 to 36 000 un ts t m l ly

B for I ll w v lable

that the septic and toxic types may occasionally coexist in which cases the outlook is particularly grave

Wound or "Surgical" Scarlet Fever When hemolytic streptococci enter a break in the skin or mucous membranes and multiply they may liberate erythrogenic toxin If this takes place in an individual susceptible to the toxin the typical rash of scarlet fever will develop The portal of entry may be a wound a burn a surgical incision the umbilical cord of the newborn infant or the postpartum uterus Since all these conditions are obviously not surgical we prefer to use the term wound scarlet fever to distinguish this variety from the scarlet fever which occurs as a result of pharyngitis Other than the portal of entry there is no difference in the two conditions The prognosis in each case is dependent upon the severity of the disease at the primary site plus the degree of general toxicity

COMPLICATIONS

Table 33 shows the incidence of the more common complications in 31 655 cases of scarlet fever collected from the literature These patients were treated before the advent of penicillin and the sulfonamides Although no similar figures can be compiled for streptococcic sore throat without rash it has been observed that when the two conditions existed side by side as in food borne epidemics the complications were similar [22] It is our opinion that the complications of streptococcic sore throat are essentially the same as those occurring in scarlet fever with the exception of those found in the skin as sequels of the rash

TABLE 33

INCIDENCE OF THE MORE FREQUENT COMPLICATIONS OF SCARLET FEVER IN 31 655 COLLECTED CASES

Complication	*Incidence (per cent)*
Cervical lymphadenitis	25.5
Rhinitis and sinusitis	4.6
Otitis media	16.7
Arthritis	2.8
Acute mastoiditis	2.4
Acute nephritis	1.8

Before penicillin and sulfonamides became available

Cervical lymphadenitis was noted in 25.5 per cent of all cases All degrees of tenderness and swelling may occur on one or usually on both sides of the neck Occasionally one of the lymph nodes may suppurate

Rhinitis and sinusitis were observed in 21.6 per cent of patients Simple rhinitis is found more often especially in children The maxillary sinuses are usually involved the frontal and ethmoidal sinuses less often and the sphenoidal sinuses least frequently of all Sinusitis is often severe in young children and may be fatal Meningitis may follow especially when the frontal or sphenoidal sinuses are affected

Otitis Media Extension along the eustachian tube to the middle ear occurs so easily in young children that otitis media is encountered frequently in patients under five years of age and nearly as often in children between the ages of five and fifteen It is also observed occasionally in adults It was present in 16 7 per cent of patients of all ages in the collected series Once the infection has reached this point it may proceed farther and cause acute mastoiditis (in 2 4 per cent of all patients) Rarely it may even cause meningitis

Pain is the dominant symptom in otitis media It may be a dull ache or sharp and excruciating It is often accentuated with each heart beat Partial deafness and fever of from 1 to 5 degrees are also present On examination auricular tenderness may be found The eardrum shows congestion especially around the edges and along the malleus in the early stage and later shows inflammation throughout its extent along with partial or complete obliteration of the landmarks A horizontal line across the tympanic membrane denotes fluid in the middle ear Drops of exudate or hemorrhagic blebs may appear on the drum If there is sufficient exudate the membrane will bulge outward

Mastoiditis should be suspected if the temperature is high or signs of general toxicity are pronounced or if there is a persistent purulent discharge from the middle ear Older children will report pain and tenderness over the mastoid process Swelling of the soft tissues behind the ear is usually present A roentgenogram will show congestion or decalcification of the mastoid cells

Other *less frequent complications by extension* are peritonsillar abscess (quinsy) retropharyngeal abscess and cellulitis of the neck

Among the structures affected elsewhere in the body the joints are most frequently involved *Arthritis* was noted in 2 8 per cent of the collected cases Sometimes there are only fleeting migratory joint pains Less frequently there is an effusion into a joint space and rarely suppuration This complication will be discussed more fully under Rheumatic Fever (pp 163 to 172)

Nephritis Evidences of renal irritation are present in most patients with streptococcic sore throat and scarlet fever Usually these comprise no more than albuminuria with a few hyaline casts Such abnormalities are presumably associated with albuminous degeneration (cloudy swelling) of the kidney tubules and may be classified as a toxic nephrosis This syndrome begins early in the course of the infection and clears up as the other manifestations of the disease disappear

True glomerulonephritis on the other hand although it may begin while the rash is still present usually starts after the tenth day of the disease The onset may be acute with scant urine smoky or red in color containing hyaline and granular casts and red and white blood cells Edema may be generalized convulsions may occur and even death may supervene within a few days Many cases are milder with symp-

toms appearing gradually Oliguria may be noted first or a little edema of the face accompanied by the characteristic urinary abnormalities The disease may progress until it becomes severe or it may remain mild and improve within a few days or weeks A relatively small proportion of patients with acute nephritis continue to have chronic nephritis Whether the latter form will occur or not cannot be predicted from the severity of the initial phase Consequently even the slightest manifestations of nephritis should be considered potentially serious

A number of cases lie somewhere between the syndrome of toxic nephrosis and definite glomerulonephritis The urine of these patients contains in addition to albumin red blood cells hyaline and granular casts and perhaps an abnormal number of leukocytes On the other hand the patients exhibit none of the systemic manifestations of nephritis This condition has been called focal nephritis but with little reason It may represent an exaggerated phase of renal irritation or toxic nephrosis or it may be a mild or subclinical phase of glomerulonephritis

Other complications which may occur as a result of transmission of *streptococci to various parts of the body are pneumonia erysipelas* meningitis osteomyelitis pyelitis and peritonitis Serous meningitis and encephalitis are infrequently seen Paronychia sometimes results from an infection introduced during the process of peeling Purpura is a rare complication with a high fatality rate Rheumatic fever will be discussed in a separate section beginning on page 163

RECURRENCE AND REINFECTION

Since there are numerous types of hemolytic streptococci it is obvious that many individuals develop several streptococcic infections during a lifetime If the organism responsible for any one of these infections generates erythrogenic toxin and the individual is susceptible to the toxin he may develop scarlet fever if the organism does not develop a sufficient amount of the toxin or if the individual is not susceptible to it a streptococcic sore throat will result It has long been noted that during convalescence from scarlet fever patients on open wards often develop pharyngitis Allison and Brown[1] and others have shown that this is usually an infection with a different type of streptococcus (obtained through contact with another patient on the ward) rather than a recurrence of the patient s original infection If the patient has not developed a sufficient immunity to the erythrogenic toxin he may develop the scarlatinal rash also although *in most instances a sore* throat alone develops Many other late complications instead of being due to the original type of streptococcus undoubtedly result from contact infections

LABORATORY AND SPECIAL EXAMINATIONS

The *leukocyte count* is usually elevated to levels as high as 20 000 per cu mm Rarely higher counts up to 50 000 per cu mm have been

seen In milder cases the leukocyte count may be within normal limits There is a relative increase in the granulocytes with a shift to the left

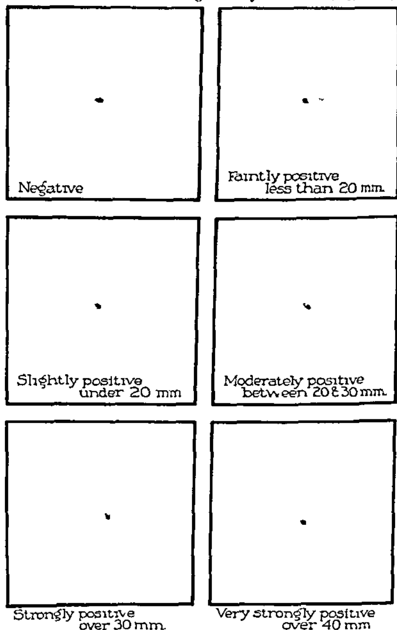


Fig 18 Positive and negative reactions to the Dick test (From Dick and Dick Scarlet Fever Year Book Publishers Inc Chicago Ill)

of the Schilling index When a scarlatinal rash is present eosinophilia may occur during defervescence

Cultures taken from the pharynx will show the *Streptococcus haemo-*

lyticus almost invariably a strain belonging to Group A These organisms will usually be present in pure culture in the severely ill patients but may comprise only one-third to three-fourths of the colonies on the blood agar plate in patients with mild and moderately severe illnesses

The *Dick test* consists in the intracutaneous injection of 0 1 cc of Dick toxin containing one skin test dose of the toxin The test should be read in twenty four hours at which time a positive test (indicating that the individual is susceptible) should show an area of redness at least 1 cm in diameter *When the test is negative (indicating an immune*



Fig 19 A positive Schultz-Charlton reaction showing blanching of the rash at the site where antitoxin has been injected (From Dick and Dick Scarlet Fever Year Book Publishers Inc. Chicago Ill)

individual) there is a smaller area of redness or none at all (Fig 18) This test is usually positive before an individual develops scarlet fever *and becomes negative during the course of the disease within a week or* ten days as a rule While this sequence of events generally takes place it is by no means infallible Dick negative individuals have been known to develop scarlet fever and on the other hand patients have gone through an attack of scarlet fever and remained Dick positive throughout

The Schult Charlton reaction is performed by injecting 0 1 cc of scarlet fever antitoxin or convalescent serum intracutaneously in the middle of an area where the rash which is suspected of being scarlatinal

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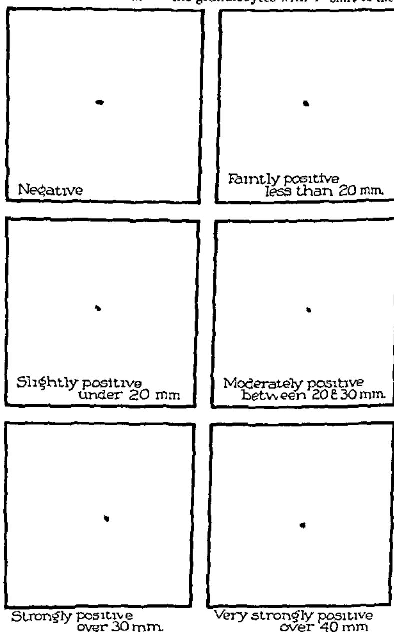


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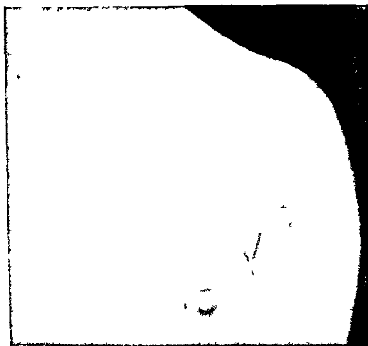


Fig 19 A positive Schultz Charlton reaction showing blanching of the rash at the site where antitoxin has been injected (From Dick and Dick Scarlet Fever Year Book Publishers Inc Chicago Ill)

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The *Schultz Charlton reaction* is performed by injecting 0 1 cc of scarlet fever antitoxin or convalescent serum intracutaneously in the middle of an area where the rash which is suspected of being scarlatinal

is heaviest Within four to eight hours an area of blanching of the rash should appear around the site of the injection if the rash is due to scarlet fever (Fig 19) This test is not infallible since blanching does not occur in all cases of scarlet fever especially if the rash is several days old

DIAGNOSIS

Clinical features helpful in the diagnosis are the history of contact with individuals having streptococcic sore throat, scarlet fever or other infections caused by *Streptococcus haemolyticus* sore throat especially if edema and exudate are present fever (sometimes with chills) vomiting and headache Diffuse fiery redness of the throat marked swelling of the tonsils and uvula and the presence of large patches of exudate are much more common in streptococcic than in any other infections of the pharynx

The rash of scarlet fever is characteristically more intense in the groins axillae and the antecubital and popliteal spaces and circumoral pallor is usually present Peeling is a late phenomenon of considerable value in confirming a questionable diagnosis It should not be relied upon entirely however since many patients with mild scarlet fever do not show any peeling and an occasional patient will exhibit this phenomenon after some other febrile or eruptive disease

Differential Diagnosis CONDITIONS SIMULATING STREPTOCOCCIC SORE THROAT The most common of these is a simple upper respiratory infection the common cold grip influenza nonspecific pharyngitis and tonsillitis In general in these conditions the throat is not very sore in comparison with the other symptoms inflammation of the pharynx is not so diffuse edema is less frequent and less marked when present exudate if it occurs at all is usually scant and in small patches and cervical lymphadenitis is seldom present The milder cases of streptococcic sore throat however are indistinguishable in appearance from those found in other infections so that when no rash is present it is impossible to diagnose them definitely without resorting to throat cultures[5]

The throat in a patient with diphtheria may be confused with that found in a patient with streptococcic pharyngitis In diphtheria the onset is usually insidious the temperature is relatively low in proportion to the elevation of the pulse rate and the evidences of toxicity the pharynx is purplish rather than fiery red the tongue does not have enlarged papillae The membrane of diphtheria is tenacious while the exudate in the streptococcic infection can be wiped off without difficulty Culture of the pharynx for virulent diphtheria bacilli is the only certain confirmation of the presence of this disease and should always be done if there is any doubt

In Vincent s angina there are patches of grayish white pseudomembrane each with a border of red inflamed mucous membrane but separated from other patches by healthy tissue Removal of a patch

leaves an ulcerated area which bleeds freely In most instances ulcers are also present on the gums or on the buccal mucosa The diagnosis is confirmed by finding the typical Vincent s spirochetes and fusiform bacilli in a stained smear

CONDITIONS SIMULATING SCARLATINAL RASH Drug rashes are often indistinguishable from that of scarlet fever They may follow administration of the sulfonamides aspirin quinine atropine and other drugs When the drug has been given for the treatment of a sore throat the diagnosis is doubly difficult A history of the medication received and of previous drug sensitivities is most valuable The absence of enanthem strawberry tongue circumoral pallor and of Pastia s lines is helpful though not conclusive A positive Schultz Charlton reaction (i e blanching) will verify the diagnosis of scarlet fever although a negative test will not rule it out

German measles may be difficult to distinguish from scarlet fever on the first day of the disease but later the rash fades in one part of the body while appearing in another The macules in German measles are usually more discrete than in scarlet fever the pharyngeal signs less marked and postauricular and occipital lymph nodes are palpable When the clinician is in doubt it is best to isolate the patient as if he had scarlet fever for a day or two by which time the diagnosis will have become more certain

In measles the papules are discrete they may become confluent in some areas but this is never true over the entire body The rash is found on the face and scalp and is not accentuated in the axillae groins popliteal and antecubital spaces Although conjunctivitis and rhinitis are present pharyngeal signs are minimal Koplik s spots present in a patient establish the diagnosis of measles

Prevention

Active Immunization The rash of scarlet fever and some of the toxic symptoms can be prevented in a fair proportion of susceptible persons (persons with a positive Dick test) by active immunization with erythrogenic toxin Subcutaneous injections of 650 2500 10 000 30 000 and 100 000 skin test doses at weekly intervals are recommended Two weeks after the last dose the Dick test should be performed again If it is still positive the fifth dose should be repeated These injections are often followed by local or general reactions Since they do not produce immunity against infections by the streptococci themselves but only against the effects of the erythrogenic toxin and since this limited amount of immunity is not obtained in all subjects active immunization is limited to children and to hospital personnel coming into frequent contact with streptococcic infections

Sulfonamides In epidemics all the individuals in a group may be given sulfonamides such as sulfadiazine in doses of 0 5 gm ($7\frac{1}{2}$ grains)

twice a day This will decrease the number of carriers although the number will rise again when the administration of sulfonamides is stopped Because of the danger of establishing sulfonamide resistant strains of streptococci this method of prophylaxis should be used only under special circumstances in a limited group of persons and for a period of not more than three or four weeks

Penicillin Although the administration of sufficiently large doses of penicillin will cause the disappearance of hemolytic streptococci from the throats of most individuals (see below) this antibiotic is not recommended for prophylaxis because of the possibility of the production and dissemination of penicillin resistant strains

Prognosis

The prognosis in streptococcic sore throat is difficult to determine since an insufficient number of cases has been studied in which the etiologic agent has been positively identified The largest groups have been observed in milk borne epidemics Here the case fatality rates have averaged slightly over 2 per cent Among the endemic cases of streptococcic pharyngitis most of which are much milder than those in epidemics deaths are rare although they do occur as a result of complications

The case fatality rates in scarlet fever have been more extensively studied They depend in the main upon two factors the severity of the disease and its complications and the age of the patient As in other infectious diseases the death rate is higher in infants and very young children than in older children and adults For some unknown reason the fatality rate from this disease has decreased considerably since the beginning of this century It now averages somewhere between 1 and 2 per cent

Treatment

Hospitalization and Isolation In a mild or moderately severe case the patient is usually as well off at home as in a hospital where he runs the chance of secondary infection with other organisms If complications appear which may require surgical attention the patient is better off in the hospital

Patients with streptococcic sore throat whether accompanied by a rash or not should be isolated until the clinical manifestations of the acute pharyngitis have disappeared and as long thereafter as local health department rules require

Penicillin Treatment of Scarlet Fever Penicillin has shown a powerful antibacterial effect on the hemolytic streptococcus in vitro and in patients infected by this organism We[9] found that when penicillin was administered to patients with scarlet fever it resulted in (1) a fairly rapid fall in the temperature (Figs 20 and 21) with concomitant diminution in toxicity and other general symptoms (2) disappearance of

the hemolytic streptococci from the throat of nearly every patient and (3) a diminution in the number of pyogenic complications

As shown in Table 31 the duration of fever averaged fifty two hours after penicillin therapy was started compared with twenty seven hours in patients given antitoxin ninety-one in those who received sulfonamides and ninety nine hours (after admission to the hospital) in patients treated symptomatically This is what would be expected in view of the fact that penicillin does not neutralize the erythrogenic toxin (see p 70)

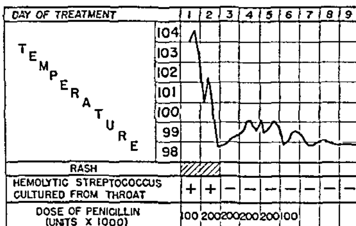


Fig 20 Temperature chart of a patient with scarlet fever showing rapid subsidence of fever and rash after penicillin therapy

E. H. a Negro child aged three years had abdominal pain three days before admission followed by listlessness, anorexia fever and vomiting Physical examination showed a typical scarlatinal rash and strawberry tongue Both tonsils were enlarged inflamed and covered with a follicular exudate The pharynx was intensely red The leukocyte count was 30 000 per cu mm. Penicillin N was administered in doses of 0 000 units every six hours. The rash receded and the temperature dropped within twenty four hours, and hemolytic streptococci could no longer be cultured on the third day of hospitalization There were no further symptoms except a few days of low grade fever

as does antitoxin but reduces the number of or eliminates entirely the hemolytic streptococci in the pharynx thus causing the toxin production to stop The time required for this process would obviously be longer than the time necessary to neutralize the toxin directly In view of this fact we recommend (Table 32) that patients with severe toxic symptoms be given full doses of antitoxin or convalescent serum in addition to penicillin Failure of a patient to improve within twenty four to forty eight hours of the start of penicillin therapy is most likely due to the fact that the streptococcus in his throat is relatively resistant to penicillin Such a situation should be met by doubling or tripling the dose of penicillin At the same time if the patient is very ill he should also be given convalescent serum or antitoxin

We have confirmed in scarlet fever patients the observation of Plummer[18] that in patients with sore throat due to hemolytic streptococci

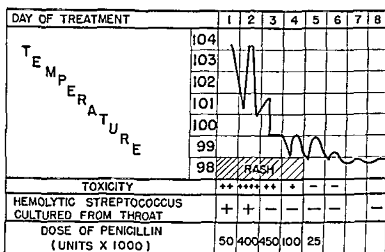


Fig 21 Temperature chart of a patient with scarlet fever showing moderately rapid subsidence of fever rash and toxicity after penicillin therapy

I D a Negro girl aged eight years had fever sore throat rash and stiff neck twenty four hours before admission Physical examination showed the typical rash of scarlet fever with a fiery red throat and follicular tonsillitis Lumbar puncture revealed no abnormalities Penicillin G was given in doses of 50 000 units every four hours for five doses When there was no improvement this was increased to 50 000 units every two hours Fourteen hours after the dose was increased the temperature began to fall Later the dose was decreased and then stopped altogether on the fifth day of treatment Toxicity and rash had disappeared by the fifth day Hemolytic streptococci could not be cultured from the pharynx after the second day

TABLE 34

COMPARISON OF THE RESULTS OF THE TREATMENT OF SCARLET FEVER WITH PENICILLIN ANTITOXIN SULFONAMIDES AND SYMPTOMATIC MEASURES

Method of Treatment	*No of Patients*	*Duration of Fever after Admission* (hours)	*Incidence of Complications Developing after Admission* (per cent)	*Incidence of Throat Cultures Positive for Hemolytic Streptococci during Convalescence* (per cent)
Penicillin	150	52	4	6
Antitoxin	25	27	44	85
Sulfonamides	25	91	15	45
Symptomatic*	1[illegible]3	99	28	8[illegible]

* Patients treated in this manner had temperatures below 101 F mild toxicity and no complications

these organisms reappear and are accompanied by a return of the sore throat fever and general symptoms if penicillin therapy is discontinued too soon (Fig 22) Accordingly we recommend that patients be treated

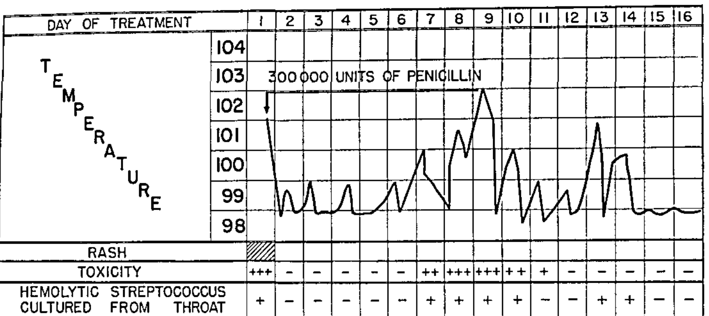


Fig 2 Temperature chart of a patient with scarlet fever showing temporary response to a single dose of penicillin followed by relapse and subsequent recovery

F H a Negro boy aged four years had anorexia sore throat and headache for four days before admission followed by rash two days before admission Physical examination showed considerable enlargement and redness of the tonsils slight injection of the pharynx a red tongue with elevated papillae and a typical scarlatinal rash One intramuscular injection of 300 000 units of penicillin X was followed by a drop in the temperature to nearly normal limits within twelve hours At the same time the rash the toxicity and the pharyngeal inflammation subsided On the second day hemolytic streptococci could no longer be obtained in throat cultures After five days the temperature rose again the patient became toxic redness of the throat returned and hemolytic streptococci reappeared in the pharyngeal culture Thirty four hours later a gradual defervescence began and the other abnormal signs gradually disappeared

for at least five days or until the temperature has been normal for forty eight hours and purulent complications have been eradicated

Our patients have received 25 000 units of penicillin intramuscularly or 100 000 to 125 000 units by mouth every three hours Smaller doses of 15 000 units every three hours intramuscularly would probably be sufficient in all mild or moderately severe illnesses In the present state of knowledge of oral therapy we would not recommend doses less than 100 000 units every three hours by mouth Penicillin in oil and beeswax 300 000 units once or twice a day should also be satisfactory

Penicillin lozenges have been advocated for the treatment of streptococcic sore throat We have observed that if one lozenge of 5000 units strength is dissolved in the mouth every hour while the patient is awake recovery will occur but it will take twenty four hours longer on the average than with systemic penicillin therapy Another disadvantage of using lozenges is the possibility of producing a hypersensitivity reaction of the mucous membranes of the mouth

Penicillin Treatment of Pharyngitis Without Rash Penicillin should be given in doses of 15 000 to 25 000 units every three hours intramuscularly or 100 000 units orally every three hours or 300 000 units in oil and beeswax once or twice a day The larger doses should be used for patients with extensive pharyngitis purulent complications or considerable general toxicity

Treatment with Serum Two kinds of serum are effective in over coming the toxic symptoms of scarlet fever (1) serum from patients convalescent from the disease (preferably pooled from several patients) and (2) antitoxin developed by immunizing horses As far as ability to neutralize skin test doses of erythrogenic toxin is concerned antitoxin is far superior to convalescent serum The titer of the latter averages 500 neutralizing units per cc while antitoxin contains at least 15 000 neutralizing units in the same volume Convalescent serum however contains other substances of a protective nature probably antibacterial antibodies and antitoxins against the hemolytic leukocidic and fibrinolytic toxins of the streptococcus Furthermore it persists in the body longer than any foreign serum Most of the evidence shows that either agent will give excellent results in most cases where serum is indicated The administration of either one is usually followed by a fall in temper ture and a diminution of the toxic symptoms within twenty four to forty eight hours (Fig 23) The case fatality rate although not high in un treated cases is apparently lowered still further by serum treatment Antitoxin is used almost exclusively in patients treated at home since convalescent serum is available only in large hospitals receiving many patients with the disease or in the vicinity of a few cities where serum centers are maintained

As shown in Table 32 we recommend that the administration of con valescent serum or antitoxin be confined to patients who are toxic or

who do not respond to penicillin within twenty four to forty eight hours

Sulfonamides These drugs are not so valuable in infections of the pharynx as in other diseases caused by beta streptococci They do not affect the toxic symptoms and opinion is divided as to whether or not they diminish the complications Before penicillin was available we

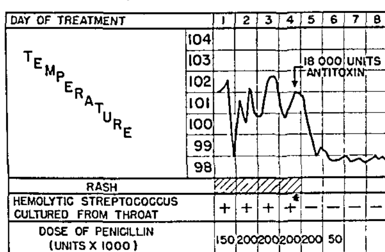


Fig 23 Temperature chart of a patient with scarlet fever showing lack of response to penicillin and prompt recovery after antitoxin therapy

Hemolytic streptococcus sensitive to 0 625 units of penicillin Highest blood concentration-0 1 6 units of penicillin

M D a woman aged twenty nine years had a sore throat six days before admission and rash and vomiting three days before There was no improvement on sulfadiazine On admission the patient appeared quite toxic There were present a generalized bright red rash general lymphadenopathy injection of the conjunctivae *moderate injection of both ear drums a strawberry tongue and a considerable* amount of reddening of the tonsils and pharynx

In spite of intramuscular injections of 50 000 units of penicillin X at six hour intervals the patient remained toxic and nauseated and the temperature did not fall On the fourth day of hospitalization 18 000 units of scarlet fever antitoxin were injected intravenously The temperature dropped to normal in twenty four hours The toxicity subsided and the rash disappeared at the same time

Subsequent studies showed that the streptococcus isolated from the patient's throat was sensitive to 0 625 units of penicillin per cc whereas the highest blood penicillin concentrations that had been obtained were 0 1 6 units of penicillin per cc It is likely that increasing the dose of penicillin may have given as good results as the administration of antitoxin

employed them only in the presence of streptococcic complications such as moderate or severe cervical adenitis otitis media mastoiditis purulent arthritis pneumonia or meningitis Sulfadiazine or sulfamerazine was preferred although sulfanilamide was used when nephritis was present since this drug does not precipitate in the urinary tract At present these compounds have been displaced by penicillin

Symptomatic Treatment. In addition to the measures which should be carried out for any patient with an acute infectious disease (see p. 15), local treatment of the sore throat will increase the patient's comfort materially. Adults will feel better after gargling every two to four hours with a solution of 0.85 gm. each of sodium chloride and of sodium bicarbonate per 100 cc. In the home one half teaspoonful of each to one glass of water may be used. Older children may be given throat irrigations of the same solution. They should not be given to children under five years of age since they may be forced into the eustachian tubes. These solutions should always be as hot as it is possible to make them without burning the patient. Continuous sips of hot water, broth, tea or milk will also diminish the soreness of the throat. Painting the throat with various highly colored solutions is of little value and may actually do harm by spreading the infection. An ice collar will lessen the pain of the swollen cervical lymph nodes. When a node enlarges sufficiently to suggest suppuration, hot compresses should be applied. The associated rhinitis should be treated by shrinking the nasal membranes with $\frac{1}{4}$ per cent neosynephrin or 1 per cent ephedrine solution used as a spray or nose drops. In young children gentle nasal suction may be needed in addition.

The patient may be allowed out of bed when his temperature has been normal for two days after a moderately severe illness, or in a severe illness after three to seven afebrile days. Since hemolytic streptococcic infections are contagious, isolation of the patient should be observed until the signs of pharyngitis have disappeared and all discharging foci have cleared up. Isolation beyond this period will sometimes be necessary because of local health regulations.

Treatment of Complications. OTITIS MEDIA. The ear drums should be examined daily in every child with streptococcic sore throat, and he should be questioned and watched for evidences of pain in an ear. An unexplained elevation of temperature should make the physician suspicious of otitis whether pain in the ear is present or not. If signs of otitis media are present, penicillin therapy should be started promptly or the dose increased if it is already being given. When indicated, the membrane should be incised to allow free drainage.

MASTOIDITIS. This should be carefully watched for whenever the ears are involved. Signs of its presence are pain, tenderness and swelling over the mastoid process. Sometimes the swelling is sufficient to push the posterior part of the ear forward and outward. The x-ray picture will show destruction of mastoid cells. Since administration of penicillin and the sulfonamides often masks the symptoms of mastoiditis, the advice of a surgeon should be sought early when this complication is suspected. If it is felt that the condition is progressing in spite of penicillin treatment, incision and drainage of the mastoid process should be performed promptly.

NEPHRITIS Keeping the patient warm and at complete bed rest until all evidences of the condition have disappeared is the most important factor in the treatment of this condition A well balanced diet and a moderate amount of fluids are usually all that are needed in addition No drugs are of any value except that there is some evidence that the patient may recover sooner if penicillin or sulfonamides are given presumably because these drugs get rid of the last vestiges of the streptococcic focus sooner than it would otherwise disappear Among the sulfonamides sulfanilamide is the drug of choice because it does not produce urinary calculi

ARTHRITIS This should be treated by immobilization and rest of the joints Fluid if present should be withdrawn and if pus is present or hemolytic streptococci are cultured from the fluid penicillin should be introduced into the joint space (see p 131)

Erysipelas

When hemolytic streptococci cause an inflammation of the superficial layers of a limited area of skin the process is called erysipelas It is caused by a number of different types of hemolytic streptococci usually belonging to Group A occasionally to Group C rarely to other groups

SYMPTOMS AND SIGNS

The onset is sudden with a chill or chilly sensations followed by a rapid rise of temperature up to 104 or 105 F sometimes as high as 106 Vomiting may be present at the onset Soon thereafter a stinging burning or itching sensation develops in the involved areas along with a feeling of tenseness and heat A sustained or remittent high fever is present in the typical case in which specific treatment is not given for about one week when it falls by crisis or rapid lysis In mild cases the temperature may not go higher than 100 to 102 F and may reach normal at some time each day Headache is frequent Delirium *is rare except in alcoholics*

Table 35 shows that 85 per cent of all erysipelas involves the head The face is more frequently affected next the ear then the back of the neck and finally the scalp least often When the face is the site of the rash the lesion usually appears first on the bridge of the nose and spreads rapidly over both cheeks usually stopping—this is a peculiar characteristic of the disease—where the skin is stretched tightly across a bony prominence Thus facial erysipelas seldom extends beyond the hair line above the malar eminences laterally and the mandibles below The affected area is raised red hot and shiny (Fig 24) On it there may be blebs containing yellow fluid or occasionally pus After the blebs rupture crusts are formed An irregular raised ridge separates it from the surrounding normal skin Where it is advancing small irregular finger like projections reach out and

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In patients who do not receive penicillin or sulfonamides the rash is usually at its height anywhere from the third to the seventh day. Thereafter, as the temperature subsides, the local lesion loses its fiery redness and gradually heals; the dead areas slough off and normal skin remains.

A primary lesion around the ear sometimes extends into the external auditory canal. If the back of the neck is the initial site, the rash does not usually advance beyond the occipital protuberance but may involve either ear or both. Involvement of the extremities, observed in

TABLE 3

PRINCIPAL AREAS OF INVOLVEMENT IN ERYSIPELAS
(COLLECTED FROM THE LITERATURE)

	Cases	Per cent of total cases	Deaths	
			Number	Per cent
Head (including face, ear and neck)	2640	85 1	[illegible]2	3 4
Extremities	31	10 0	8	9 0
Trunk	153	4 9	5	3 9
Total	3105	100 0	305	9 8

10 per cent of all patients, is likely to follow an abrasion or a scratch, a burn, a wound, whether traumatic or surgical. It may spread from a localized infection already present. Erysipelas is least frequently found on the trunk (5 per cent of all patients), although a severe form may spread from the umbilical cord in the newborn. In an occasional patient several different areas may be involved. Rarely the mucous membranes of the nose, mouth or throat may be involved, either as a primary site or by extension from the skin. The general symptoms are unusually severe in these patients and the prognosis is especially grave.

LABORATORY EXAMINATIONS

The leukocyte count is elevated anywhere from a slight amount up to 20 000 or 25 000 per cu mm. Blood cultures are positive for hemolytic streptococci in only a small proportion of all patients, but are frequently positive in fatal cases. Hemolytic streptococci may be obtained from the lesion by filling a small syringe with sterile isotonic salt solution, injecting the solution slowly just below the surface of the lesion near its edge, allowing it to remain there for a minute and then drawing it back into the syringe for culture. Fluid from a bleb is usually sterile. Hemolytic streptococci may sometimes be present in the patient's throat.

finally join together to form a new area of inflammation A varying amount of edema is present in the areas immediately adjacent to the lesion The area in the center may dry and heal while the periphery



A



B

Fig 24 Erysipelas A Third day of illness Note that definite borders are outlined and the affected portion is visibly higher than the surrounding skin area B Sixth day of illness (Courtesy of Parke Davis and Company)

is still advancing The process may extend into the nostrils Edema of the eyelids is present and may be so extreme as to close the eyes Injection of the conjunctivae and sometimes conjunctivitis occur

Erysipeloid is an infection caused by *Erysipelothrix rhusiopathiae* the organism of swine erysipelas It occurs at the site of injury usually the hand in persons handling fish or animals The lesion differs from that of erysipelas in that it is purplish red in color and advances more slowly Also constitutional symptoms are seen only in the most severe infections Erysipelas like eruptions have been observed on the legs and occasionally on the upper extremities as a result of sensitivity to dermatophytosis This condition is usually found near the fungus infection causing the sensitivity It does not have a sharp raised margin and a glazed appearance and does not spread progressively as does erysipelas Furthermore it is often present on two extremities at the same time Since these erysipelas like eruptions often recur many times it is more than likely that many of the patients in whom several attacks of erysipelas were reported to have occurred were really suffering from these sensitization phenomena due to dermatophytosis Other conditions which may be confused with erysipelas are gas gangrene (see p 121) dermatitis venenata acute eczema and urticaria

Prognosis

Among 6743 cases collected from the literature the case fatality rate was 12 9 per cent These patients were treated before the advent of the sulfonamides Among 1396 patients treated with these compounds by others and by us there have been only thirty two or 2 4 per cent deaths This does not tell the whole story The highest death rates were always in children under one year and in patients over sixty years of age When patients with erysipelas are treated with the sulfonamides practically no deaths occur except in the very young and very old and even in these groups the fatal outcome is usually due in large part to preexisting diseases or complicating conditions Penicillin is at least as effective as the sulfonamides and in view of the results obtained in other streptococcic infections is probably more effective Sufficient data are not yet available however to show whether penicillin will lower the fatality rate below that obtained with the use of the sulfonamides

Treatment

Symptomatic In addition to the general measures to be used in any severe infection (see p 15) local applications are helpful For this purpose many solutions have been advocated An iced saturated solution of magnesium sulfate or of boric acid is most commonly used It is probably the temperature of the solution that provides the relief As Osler said Perhaps as good an application as any is cold water which was highly recommended by Hippocrates

Sulfonamides In one way we can do more than Hippocrates did however for in no disease do the sulfonamides or penicillin produce

Relapse and Recurrence

Relapse occurred in about 5 per cent of patients in the presulfonamide era Since then it has been much less common The general symptoms are similar to those accompanying the initial course The local lesion may begin in the original area or in the normal skin The prognosis is slightly better and the course often shorter than in the original attack

Recurrence is more frequent in erysipelas than in most infectious diseases Three or four attacks are not uncommon and some individuals have had many more Often the same areas are involved in each attack The severity of a second or subsequent attack is not related to the seriousness of previous attacks

Complications

These may be divided into three categories (1) local and (2) systemic complications of the disease and (3) complications or associated conditions likely to occur in elderly patients who lie in bed with any severe febrile illness

In the first group come subcutaneous abscesses the most frequent of all complications Cellulitis occurs less often and gangrene of the involved area rarely Other local complications infrequently encountered are suppurative adenitis herpes labialis conjunctivitis and keratitis The systemic complications are the infections which the hemolytic streptococcus characteristically produces in various parts of the body Pneumonia is observed fairly often especially in older patients and carries a poor prognosis It may be caused by the streptococcus or by some other organism such as the pneumococcus Mild transient arthritis is not uncommon Actual suppuration of a joint from which the hemolytic streptococcus can be cultured is occasionally observed Osteomyelitis meningitis pleurisy pericarditis and endocarditis are seen less often Although albuminuria is usually present during the height of the illness true nephritis occurs in less than 1 per cent of all cases

The impact of an acute infection such as erysipelas upon the cardiovascular system of an older person may result in congestive heart failure Other complications which may occur from the enforced bed rest are decubitus ulcer phlebothrombosis and hypostatic pneumonia

Diagnosis

The distinctive appearance of the rash makes erysipelas one of the easiest diseases to diagnose The raised well defined edges the red shiny surface and the formation of vesicles are typical characteristics not usually seen in other conditions

Differential Diagnosis Cellulitis may sometimes be mistaken for erysipelas In cellulitis a nearby pyogenic focus is often found there is more induration of the lesion and the raised border is not present

merazine *Sulfonamide therapy should be continued for about three* days after the temperature becomes normal provided there are no complications which would require its continuance The temperature usually begins to fall soon after the first dose is administered and reaches normal within seventy two hours in about three fourths of the patients (Fig 25) The rash fades as the fever recedes so that the patients are well about three days sooner than those treated without benefit of chemotherapy as shown by Foley and Yasuna[6]

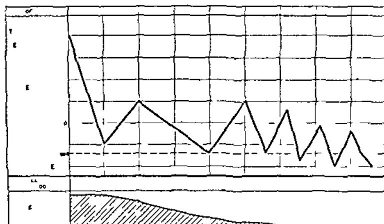


Fig 6 Temperature chart of a patient with erysipelas treated with penicillin with recovery

H N a Negro aged thirty five years had one week before admission a cold accompanied by redness of the skin around the external nares Three days before admission this area became tender and the next day the erythema spread over the cheeks the upper lip and the dorsum of the nose On admission there was a red lesion with raised sharply demarcated borders involving the nose upper lip and cheeks in a butterfly pattern The nasal mucous membranes were swollen and the pharynx was moderately inflamed The leukocyte count was 18 000 Penicillin was given intramuscularly in doses of 15 000 units every two hours for three days and then 15 000 units every four hours for the following three days The temperature fell and reached normal on the second hospital day There was slight progression of the facial lesion for the first twenty four hours after which it healed rapidly Convalescence was uneventful

Penicillin *Similar results are obtained when penicillin is administered* (Fig 26) It is the drug of choice because of the low incidence of toxic reactions which accompany its use The dose is 10 000 to 25 000 units every three hours intramuscularly *300 000 units intramuscularly in* oil and beeswax once or twice a day or 50 000 to 125 000 units orally every three hours

Other Measures A specific antiserum *made by immunizing horses* with several strains of hemolytic streptococci obtained from patients with erysipelas was formerly used with *questionable success* It has now been entirely displaced by the sulfonamides and *penicillin Ultra*

more dramatic results Sulfadiazine should be given in doses of 6 gm (90 grains) immediately followed by 1 gm (15 grains) every four hours Sulfamerazine may be given in smaller doses such as 3 gm (45 grains) initially followed by 1 gm (15 grains) every six hours

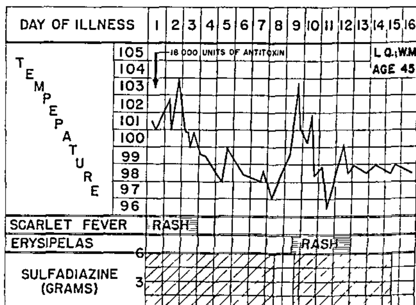


Fig 25 Temperature chart of a patient with toxic scarlet fever with recovery after antitoxin and sulfadiazine therapy followed by erysipelas with recovery

L Q a woman aged forty five years had a sore throat and a slight fever seven days before admission Two days later a rash appeared The patient became irrational on the day before admission On physical examination she was stuporous acutely ill and breathing rapidly The left ear drum was inflamed and the throat red There was a generalized erythematous rash with circumoral pallor The leukocyte count was 23 850 Therapy consisted of 18 000 units of scarlet fever antitoxin immediately by vein Since the patient had been treated with sulfonamides before admission maintenance doses of 1 5 gm of sodium sulfadiazine every six hours were given intravenously The temperature and other abnormalities subsided over the course of the next four days

Sulfadiazine therapy was stopped on the eighth day of hospitalization and on the ninth day the fever rose to 103 8 F and an erythematous area appeared over the bridge of the nose This spread bilaterally over the cheeks Sulfadiazine was again administered and the temperature toxicity and local lesion subsided over the course of the next four days

Hemolytic streptococci were cultured from the throat at this time and did not disappear on sulfadiazine therapy On doses of 200 000 units of penicillin orally every four hours the pharyngeal cultures became negative after forty eight hours Penicillin therapy was discontinued after four days and the cultures did not again become positive

Children should receive 0 03 gm (½ grain) per pound of body weight as the first dose followed by 0 06 gm (1 grain) per pound of body weight divided into six doses and administered at four hour intervals in the case of sulfadiazine and at six hour intervals in the case of sulfa

sixty six collected cases treated with sulfonamides there were only eight deaths (12 per cent) Penicillin will undoubtedly lower the fatality rate still more

TREATMENT

The treatment is by the administration of sulfadiazine sulfamerazine or penicillin preferably the last as given in detail under pneumococcic pneumonia (pp 115 to 121) Recovery from the empyema caused by this organism could only occasionally be effected by multiple aspirations without surgical drainage before the days of the sulfonamides and penicillin Since these drugs have been in use the percentage of patients requiring surgical drainage has decreased considerably With the local administration of penicillin (see p 125) and with the use of multiple aspirations alone most patients will probably recover if they are treated early

Rheumatic Fever

Rheumatic fever is a disease characterized by a variety of clinical manifestations the most common of which are arthritis endocarditis myocarditis and chorea It has been included in this chapter because according to the evidence available at the present time it is either caused by a Group A beta hemolytic streptococci or it is closely related to infection with these organisms The evidence upon which this relationship is based has been well summarized by Rantz[1] as follows

1 Rheumatic fever has been observed to follow hemolytic streptococcus infections particularly those in the respiratory tract

2 Epidemics of rheumatic fever often follow outbreaks of streptococcic sore throat

3 Recrudescences of rheumatic activity frequently coincide with reinfection with hemolytic streptococci

4 High titers of antistreptococcic antibodies and cutaneous reactions to products of hemolytic streptococci are usually demonstrable in persons with rheumatic fever

It is the generally accepted opinion that an interval of several days commonly elapses between the onset of the streptococcic respiratory infection and the appearance of the manifestations of rheumatic fever Kuttner[14] for example found that polyarthritis carditis or erythema or some combination of them appeared from nine to twenty two days after the respiratory infection began The mechanism whereby the hemolytic streptococcus produces the manifestations of rheumatic fever is generally supposed to be the development in susceptible individuals of allergy to products of the streptococci The latent period is generally thought to represent the time necessary for the production of antibodies to these organisms Recently Rantz[1] has detected evidence of continued infection (increased sedimentation rates and electro-

violet light x ray therapy tincture of iodine or silver nitrate are among the measures formerly used Most of them have proved to be useless and all have been discarded in favor of chemotherapy

Meningitis Caused by Hemolytic Streptococci

Meningitis caused by beta hemolytic streptococci is due to an extension of otitis media and mastoiditis in about three fourths of all cases Less often it follows acute sinusitis or infections elsewhere in the body Signs and symptoms of meningitis are present with the characteristic cerebrospinal fluid findings of a pyogenic infection

The *differential diagnosis* depends upon the identification of the causative agent in the cerebrospinal fluid as outlined on page 208

Treatment is with sulfadiazine or sulfamerazine and penicillin and is given in detail under pneumococcic meningitis (p 130) The results of treatment with the sulfonamides are very favorable Before these drugs were available the fatality rate among 574 collected cases was 95 per cent whereas only 31 per cent of fifty four patients treated with the sulfonamides died It is too early to assess the value of penicillin but it will undoubtedly cause further lowering of the case fatality rate

Pneumonia Caused by Hemolytic Streptococci

About 1 to 2 per cent of all cases of bacterial pneumonia are caused by the hemolytic streptococcus While it may occur as a primary disease this type of pneumonia most frequently follows a streptococcic infection elsewhere is a sequela of pneumococcic pneumonia or occurs as a complication in a patient with an entirely unrelated disease It is usually a bronchopneumonia which may involve one or more entire lobes by confluence

Clinically streptococcic pneumonia is similar in the main to pneumococcic pneumonia Frankly bloody sputum is more frequently seen in the streptococcic variety and there is more tendency to prostration and cyanosis One characteristic feature is the frequent occurrence of empyema as shown by Keefer[12] The fluid appears earlier is more often bloody and tends to remain thinner than in pneumococcic empyema

Diagnosis

Culturing hemolytic streptococci from sputum or blood is the only way to make a definite diagnosis The differential diagnosis is given on pages 110 to 115

Prognosis

The prognosis has improved greatly with sulfonamide and penicillin therapy Formerly about half of the patients died whereas among

and subtropical areas than in colder climates This is probably related to the lessened incidence of respiratory disease in warmer climates

Polyarthritis is more frequent in males than in females while chorea and probably valvular damage are more common in females

SYMPTOMS AND SIGNS

A majority of patients give a history of an upper respiratory infection one to four weeks before the onset of rheumatic fever Jones[11] found that among 160 patients the first attack was preceded by a sore throat in sixty-one cases and by a cold in thirty-one The onset of symptoms is usually acute with chilly sensations fever and joint pains although occasionally the patient experiences malaise and vague pains in the muscles and joints which gradually increase in severity and extent

Fever The temperature is usually high at the start of the attack often reaching 103 or 104° F each day and tends to fall as the other clinical manifestations diminish in severity It may remain at lower levels or be absent altogether for weeks or months while the disease is still burning on at a low rate of activity

Arthritis A migrating polyarthritis is a characteristic feature of rheumatic fever The larger joints are involved especially In descending order of frequency they are the knee ankle shoulder wrist elbow and hip Less often the smaller joints of the hand and foot are affected One or two joints may be involved at the onset from which the process may spread to other joints often improving first in the joints originally affected The typical signs of inflammation are present swelling redness heat pain and tenderness Synovial fluid may be sufficiently increased so that it can be easily aspirated When the evidences of inflammation disappear the joint is restored to normal function although in older individuals there may be pain and stiffness for several weeks more Joints which have recovered are often affected again especially if there is a fresh wave of fever and arthritis Other joints may improve partially and then become worse again In some instances on the other hand especially in younger children the arthritic manifestations are much less severe and occasionally only one joint may be involved

Carditis More important than the involvement of the joints are the cardiac manifestations of the disease since the eventual prognosis depends upon their extent and severity and the degree of residual damage The pericardium myocardium and endocardium may be affected individually or collectively Usually it is impossible to distinguish the degree to which each is involved Pericardial disease may be detected by the characteristic rub or by electrocardiographic changes (see p 167) Myocarditis may exhibit physical and roentgenographic signs of enlargement of the heart a change in quality of the first heart

cardiographic abnormalities) during the so-called latent period He suggests that when these manifestations of rheumatic activity appear sooner after a streptococcic respiratory infection than would otherwise have been expected they may be due to the development of hyper sensitivity to products of hemolytic streptococci occurring during a previous infection

On the other hand Rantz s findings can perhaps be explained as the results of pathological changes commonly present in the myocardium during the course of many acute infectious diseases Until further evidence is forthcoming it seems best to hold to the concept that a latent period following an infection with hemolytic streptococci is necessary for the development of rheumatic fever

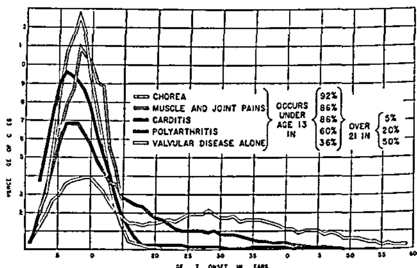


Fig 27 Rheumatic cardiac disease age distribution of first manifestations (Courtesy of Cohn and Lingg J A M A. 1?1)

Certain other characteristics of rheumatic fever have an indirect bearing on the relationship of this disease with hemolytic streptococci One of these is the age of the patient at the onset of rheumatic fever The disease usually begins during the ages when streptococcic respiratory disease is most prevalent As shown in Fig 27 the greatest number of initial attacks of rheumatic fever take place between the ages of five and ten years The disease is rare in infants although it may begin at any age even occasionally in the sixth decade [4]

The disease is more prevalent in the months from January through May or June reaching its peak incidence usually in April thus corresponding to or lagging a few weeks behind the season of the greatest number of respiratory infections It has also been observed that the disease at least in its severer forms is much less common in tropical

frequently enough in fatal cases of rheumatic fever to make it evident that lesions in the lungs are sometimes present in patients suffering from the severer form of the disease Signs of consolidation can often be detected by physical examination and bloody or blood streaked sputum may be present Bland[2] states that he has never encountered rheumatic pulmonary consolidation as an isolated phenomenon but only as a complication in patients otherwise ill with a severe type of rheumatic fever

Other Manifestations These include abdominal pain epistaxis torticollis and so-called growing pains The latter are located in the tendons behind the knee and may be accompanied by tenderness and swelling of the tendons

Recurrence Recurrences are so common in rheumatic fever as to constitute a characteristic feature of the disease Wilson[5] found that among 199 patients between the ages of four and sixteen years only 31 per cent did not experience a recurrent major attack She also observed that the longer the period of freedom from rheumatic fever after the original attack the less likelihood of a recurrence

Laboratory Examinations

Leukocyte Count In milder cases this is within normal limits although in most instances it is slightly or moderately elevated Seldom is it above 25 000 per cu mm In patients with chorea alone it usually does not go above 15 000 per cu mm

Red Blood Cells Most patients have a mild or moderately severe hypochromic anemia It is more pronounced in the more severe and long-standing cases

Sedimentation Rate This test is most valuable for the determination of the activity of rheumatic fever It is usually elevated during the active stages of the disease and may remain above normal values for some time after fever leukocytosis and other evidences of infection have subsided On the other hand in some instances fever leukocytosis or both may be present for a period of time after the sedimentation rate has returned to normal levels In mild cases the sedimentation rate may not be elevated at any time

Electrocardiographic Changes Abnormalities which may be found in the electrocardiograms when active rheumatic carditis is present are prolongation of the PR or QT intervals inversion of the T waves ST deviation broadening of the P waves or of the QRS group premature contractions ectopic tachycardia auricular fibrillation Pericarditis may be manifested by low voltage in all the standard leads Lengthening of the PR interval broadening of the QRS group or inversion of the T waves are most commonly observed None of these abnormalities however is diagnostic and all therefore must be considered in conjunction with the other manifestations of the disease

sound tachycardia gallop rhythm and a systolic apical murmur due to dilatation of the left ventricle of the mitral valve rings or of both Less frequently auricular fibrillation or complete heart block is present Depending upon the degree to which cardiac function is disturbed signs of congestive failure may be present dyspnea orthopnea cyanosis edema rales at the lung bases enlargement of the liver and peripheral edema These manifestations may all appear within twenty four hours in fulminating cases or may build up gradually over the course of several weeks

Endocarditis Although mural endocarditis occurs the most common rheumatic lesions are on the valves themselves The mitral valve is almost invariably affected the aortic in approximately one half of the cases the tricuspid in one-third and the pulmonary valve rarely The characteristic murmurs indicating involvement of these valves will be heard Systolic murmurs however cannot be considered diagnostic of valvulitis until they have been observed to remain after the active infection subsides Even soft blowing diastolic murmurs sometimes disappear when the active phase is past

Chorea Chorea is more closely restricted to children between the ages of five and fourteen years than are the other manifestations of rheumatic fever It is infrequent in patients above the age of nineteen years except in pregnant women It may be present alone or may be accompanied by other manifestations of rheumatic fever When other manifestations were not present chorea was accompanied by signs of rheumatic heart disease in 28 8 per cent of 526 cases [8] whereas when other signs of rheumatic fever were present along with the chorea 71 6 per cent of 836 cases had manifestations of rheumatic involvement of the heart Chorea is rarely fatal and although it may last for months appears to be self limited

Subcutaneous Nodules These are flat nodules 1 to 10 mm in diameter which are connected with the fibrous tissue below the skin and are found over bony prominences especially those of the hands wrists and fingers but also the elbows knees ankles vertebrae the spine of the scapula and the olecranon process They are hard non tender and can be moved independently of the skin They may appear in successive crops and persist for varying periods of time

Dermatoses Several types of cutaneous manifestations form a part of the rheumatic state including erythema annulare erythema marginatum erythema nodosum and purpuric rashes All except perhaps erythema marginatum may occur under other circumstances in the absence of rheumatic fever so that their presence is not certain evidence of the disease

Pulmonary and Pleural Manifestations Pleurisy is present in 5 to 10 per cent of patients It may be dry or less frequently may be accompanied by an effusion Pulmonary consolidation has been found

frequently enough in fatal cases of rheumatic fever to make it evident that lesions in the lungs are sometimes present in patients suffering from the severer form of the disease. Signs of consolidation can often be detected by physical examination and bloody or blood-streaked sputum may be present. Bland[4] states that he has never encountered rheumatic pulmonary consolidation as an isolated phenomenon but only as a complication in patients otherwise ill with a severe type of rheumatic fever.

Other Manifestations. These include abdominal pain, epistaxis, torticollis and so-called growing pains. The latter are located in the tendons behind the knee and may be accompanied by tenderness and swelling of the tendons.

Recurrence. Recurrences are so common in rheumatic fever as to constitute a characteristic feature of the disease. Wilson[5] found that among 199 patients between the ages of four and sixteen years only 31 per cent did not experience a recurrent major attack. She also observed that the longer the period of freedom from rheumatic fever after the original attack the less likelihood of a recurrence.

LABORATORY EXAMINATIONS

Leukocyte Count. In milder cases this is within normal limits although in most instances it is slightly or moderately elevated. Seldom is it above 25,000 per cu. mm. In patients with chorea alone it usually does not go above 15,000 per cu. mm.

Red Blood Cells. Most patients have a mild or moderately severe hypochromic anemia. It is more pronounced in the more severe and long-standing cases.

Sedimentation Rate. This test is most valuable for the determination of the activity of rheumatic fever. It is usually elevated during the active stages of the disease and may remain above normal values for some time after fever, leukocytosis and other evidences of infection have subsided. On the other hand in some instances fever, leukocytosis or both may be present for a period of time after the sedimentation rate has returned to normal levels. In mild cases the sedimentation rate may not be elevated at any time.

Electrocardiographic Changes. Abnormalities which may be found in the electrocardiograms when active rheumatic carditis is present are prolongation of the PR or QT intervals, inversion of the T waves, ST deviation, broadening of the P waves or of the QRS group, premature contractions, ectopic tachycardia, auricular fibrillation. Pericarditis may be manifested by low voltage in all the standard leads. Lengthening of the PR interval, broadening of the QRS group or inversion of the T waves are most commonly observed. None of these abnormalities, however, is diagnostic and all therefore must be considered in conjunction with the other manifestations of the disease.

Diagnosis

Since no feature of the disease is pathognomonic the diagnosis rests upon the proper interpretation of the various manifestations present in a patient The problem has been well discussed by Jones[10] who has divided the manifestations of the disease into major and minor as follows

Major Manifestations

Carditis	Subcutaneous nodules
Arthralgia	Recurrences of rheumatic fever
Chorea	

Minor Manifestations

Fever	Epistaxis
Abdominal pain	Pulmonary findings
Precordial pain	Laboratory findings
Rashes	

He felt that a combination of the major findings made the diagnosis of rheumatic fever reasonably certain while even a combination of the minor findings without the presence of at least one of the major manifestations is no more than suggestive of the disease

Mild forms of the disease occur which cannot be diagnosed by these criteria While it is important that the physician should not pin a label of rheumatic fever upon a patient without sufficient evidence it is also necessary for him to realize that patients with this disease may exhibit no more than malaise lassitude anorexia and slight fever Rheumatic fever must be suspected and its characteristic manifestations searched for repeatedly in any child or young adult with such a picture

Differential Diagnosis Other diseases which may be confused with rheumatic fever because of joint manifestations include gonococcic arthritis acute rheumatoid arthritis Still s disease sickle cell anemia brucellosis shigella dysentery serum sickness and less frequently hemophilia scurvy and gout The diagnosis of gonococcic arthritis *will be greatly aided by culturing the organisms from urethral or* cervical discharges from the blood or synovial fluid or by obtaining a *positive complement fixation test*

Acute rheumatoid arthritis more often involves the vertebrae and the small joints such as those of the hands and feet and may exhibit clinical or x ray evidence of bony changes as a result of previous attacks

The arthritis of brucellosis or dysentery must be diagnosed by culture of the organisms from the blood lymph nodes or stools in the first disease and from the stools in the second In addition agglutination tests and intracutaneous tests are most helpful in diagnosing brucellosis The other conditions mentioned should offer no trouble if they are borne in mind and appropriate studies carried out

Systolic murmurs are often erroneously considered to be evidences of rheumatic fever Most diastolic murmurs and loud long apical

systolic murmurs which are transmitted over a wide area are likely to be rheumatic in origin if they occur in conjunction with other evidences of rheumatic fever It is best however to obtain electrocardiographic evidence of active myocarditis whenever possible

PROGNOSIS

As far as immediate recovery is concerned the prognosis is good since only about 1 to 4 per cent of the patients die during the acute infection The eventual prognosis on the other hand is poor Wilson[4] found that among children who had evidences of active carditis 36 per cent died during childhood and one-half although they survived during this age period developed mitral stenosis often with aortic insufficiency and with moderately to markedly enlarged hearts The picture was somewhat more encouraging in the patients who did not have recognizable active carditis since only 0 5 per cent of these died during childhood less than one third developed mitral stenosis and only 4 per cent developed markedly enlarged hearts

TREATMENT

Salicylates No therapeutic agent is available which will alter the fundamental course of the disease Salicylates given as acetylsalicylic acid or sodium salicylate will usually bring about diminution in pain and swelling of the joints and subsidence of the fever There is no definite evidence that they prevent or ameliorate the cardiac complications Large doses of these drugs are usually well tolerated by children In the majority of cases they can be administered orally in doses of 1 to 1 5 gm (15 to 22½ grains) every four hours In order to diminish gastric irritation 1 gm (15 grains) of sodium bicarbonate should be given with each dose or else food should be given before each dose If the salicylates cannot be given orally they may be administered by rectum in doses of 4 to 6 gm (60 to 90 grains) in 200 cc of water at eight hour intervals

The intravenous route has been recommended by several workers especially with the employment of massive doses of salicylates It seems to us that the danger from toxic reactions far outweighs any possible advantages of such a method

Aminopyrine Although this drug is effective in smaller doses 0 3 to 0 5 gm (5 to 7½ grains) every four hours it is not recommended for routine use because of its tendency to cause agranulocytosis It may be reserved for the occasional case in which the response to salicylates is not satisfactory

Rest During the active stage of rheumatic fever the patient should be kept in bed When the fever has subsided completely and the signs and symptoms of the disease are gone the physician should make sure that the sedimentation rate and the leukocyte count have returned to

normal levels before he allows the patient to start getting up It is important that the administration of salicylates be discontinued for some time before the decision is made to allow the patient to get out of bed since the disease may merely be quiescent in the presence of salicylates and will become active again when they are not being administered If congestive heart failure is present the amount of activity allowed must be determined by the cardiac condition In any case the patient s return to normal life should be gradual and continual checks should be made for evidences of active rheumatic fever or of congestive heart failure

Diet and Vitamins During the periods when high fever is present the diet should be composed mostly of liquids including milk fruit juices and creamed soups When the patient can tolerate a solid diet it should contain adequate amounts of protein and an abundance of carbohydrates It is best to supplement this with vitamins Although there is no evidence that vitamin C deficiencies are etiologically related to rheumatic fever nevertheless the vitamin C content of the tissues may be lowered in this disease as it is in many acute infectious diseases It is accordingly advisable to administer 100 mg of this vitamin a day to rheumatic fever patients

Digitalis As in other diseases digitalis should be given only for congestive heart failure or for auricular fibrillation The methods of administration are the same as those used under other circumstances

Other Measures The use of streptococcic vaccines or serums or of nonspecific fever therapy has been abandoned as worthless in all phases of rheumatic fever with the exception of chorea Likewise the sulfonamides and penicillin do not exert any beneficial effect upon the disease itself In fact there is some question as to whether the sulfonamides may not actually increase the severity of the symptoms

Treatment of Chorea In mild and moderately severe cases of chorea, bed rest in a quiet environment is often followed by improvement If necessary to obtain rest sedatives such as phenobarbital or bromides should be given in small doses throughout the day In severe cases barbiturates may be needed Even morphine or inhalation anesthetics may be required to diminish the excessive motion

Fever therapy induced either by intravenous injections of typhoid vaccine or by a fever cabinet has been used with success in intractable cases High temperatures from 104° to 106° F apparently give the best results

The diet should be nutritious and should contain adequate amounts of vitamins In severe cases the patients may have to be fed

Prevention of Further Attacks

Since rheumatic fever is characterized by recurrences and since each successive attack increases the possibility of severe cardiac damage it

is of the utmost importance that recurrences be prevented if possible Several measures have been tried

Tonsillectomy Removal of the tonsils was advocated frequently in the past but the present consensus is that the tonsils should never be *removed during the acute stage of the disease and after recovery only if they are diseased In other words they should be removed if they* are likely to be injurious to the general health of the patient whether he has rheumatic fever or not

Change of Climate Removal to a warm climate will diminish the possibility of acquiring streptococcic infections and may thus prevent *recurrences of rheumatic fever In order to have any chance of success* however such a procedure would require that the child remain continuously away from his former home for many years Since expense and other considerations usually make this impossible the physician would do well to try all other feasible methods for prevention of recurrences before advising anything so drastic

Sulfonamides *The most promising method for the prevention of subsequent attacks is the employment of small doses of sulfonamides* These drugs diminish the frequency of upper respiratory tract infections with hemolytic streptococci as shown by the experiences in the armed forces during World War II[29] While it is true that sulfonamide prophylaxis when used on a large scale eventually resulted in the *propagation of sulfonamide resistant strains of hemolytic streptococci* such strains are less likely to appear and would certainly be spread less readily when only a relatively few individuals in a community were receiving the drugs

Although sulfanilamide was first used for this purpose[3, 4] sulfadiazine is more effective against the hemolytic streptococcus and is less toxic It is therefore the drug of choice Sulfanilamide sulfathiazole *or sulfamerazine may be used however A dose of 0 5 gm should be* given twice a day for the months from September through June inclusive until the child has been free of active infection for three years or at least until he reaches the age when the incidence of recurrences begins to diminish (usually around the age of eleven or twelve years) Some investigators believe that the drug should be given throughout the year

The patients should be seen at weekly intervals at first and later at least every month *The parents should be instructed to be on the* lookout for rash or fever or for the development of undue weakness If rash or fever appears the sulfonamide should be stopped until it is gone at which time another sulfonamide should be substituted (see p 52) Since weakness may indicate anemia or agranulocytosis a leukocyte count and hemoglobin estimate *should be made when it* appears *If either is present the drug should be stopped and proper measures taken to restore the blood to its normal state* If sulfonamide

prophylaxis is still desirable another sulfonamide may be employed although repeated blood counts should be taken for the first few months of administration If these details are attended to there should be little danger of serious consequences from the long-continued administration of these drugs

Other Measures The claim has been made occasionally that the administration of salicylates will prevent recurrences of rheumatic fever but there is no convincing proof that this is true

The patient s general health should be brought up to and kept at the highest peak possible This requires sufficient amounts of proteins and vitamins

(References will be found on page 183)

9 *Streptococcic Infections*

Infections with Nonhemolytic Streptococci

(Alpha and Gamma Streptococci)

The alpha and gamma streptococci by themselves seldom cause infections in human beings When the local or general resistance of the host has been lowered then these organisms join with others in the mixed infections which supervene as in the hypostatic pneumonias which occur in bedridden patients or the pneumonias complicating the postoperative atelectases These nonhemolytic streptococci may sometimes fasten themselves onto an area of damaged tissue and start there a slow persistent multiplication which gradually wears out the reparative processes of the host and causes death This is what happens in most cases of bacterial endocarditis

Endocarditis Caused by the Nonhemolytic Streptococci (Subacute Bacterial Endocarditis)

The endocardium is ordinarily not attacked by bacteria even though millions of them are sloshed across the valves during a bacteremia Occasionally however bacteria with highly invasive properties or (when the valves have been previously damaged or are congenitally abnormal) the less virulent ones may attach themselves to a valve and multiply Such a process is called endocarditis When it occurs within a patent ductus arteriosus it is called endarteritis When the organisms proliferate slowly and the disease is prolonged over weeks or months it is called subacute bacterial endocarditis (or endarteritis) In most instances the subacute variety is caused by nonhemolytic streptococci and attacks only previously damaged or abnormal valves These principles do not always hold true however Nonhemolytic streptococci *sometimes attack valves which are apparently normal* A slowly progressive endocarditis may occasionally be caused by a gonococcus a staphylococcus or other organisms while a nonhemolytic streptococcus may sometimes be responsible for a fulminating infection Furthermore in a patient who seems destined to suffer from the disease for many months death may occur suddenly within a few days from an embolus lodging at a vital point Consequently it is best to designate the endocarditis according to the infecting organism instead

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and feet and especially in the pulp of the fingers and toes. Embolism to the brain may cause monoplegia or hemiplegia. If an embolus lodges in the spleen, there is sharp pain over that organ and tenderness on palpation, sometimes accompanied by a friction rub. When an embolus lodges in a kidney, the pain in the region of the flank may be accompanied by hematuria. Vegetations on the right side of the heart may throw off emboli which will cause pulmonary infarction. Emboli may also lodge in the mesentery or elsewhere in the abdomen, in the arteries to any of the extremities or elsewhere.

Other Manifestations. The spleen was enlarged in 59 per cent of Kelson's cases. Enlargement usually begins early and increases as the disease progresses. The spleen is sometimes tender, especially after an embolus has lodged there, and occasionally a friction rub may be present.

Generalized enlargement of the lymph nodes is occasionally found. In long-continued infections the skin often takes on a light brown color resembling coffee mixed with an abundance of cream (*cafe au lait* color). Clubbing of the fingers appeared in 16.7 per cent of Kelson's patients. Clubbing of the toes was *also* seen in patients before the days of penicillin.

Course

There may be one or more spontaneous remissions, during which the patient is afebrile and asymptomatic, but before the modern era of antibiotic therapy the disease almost invariably returned and slowly and relentlessly marched the patient to his grave. The victim became thinner, paler and weaker; showers of emboli were released from time to time; a cerebral accident, meningitis, septic pulmonary infarctions or congestive heart failure supervened in some instances, until death's merciful intervention put an end to the uneven struggle. Among Kelson's 250 patients, who were all treated before the advent of penicillin, 87 per cent died within nine months of the onset, and the longest duration was nineteen months.

Laboratory Examinations

Blood cultures are the most important laboratory aid. Since it is important to confirm a single positive blood culture (which might be due to a contaminant), it is advisable to take at least three successive cultures at intervals of one hour. These will usually provide both a diagnosis and a confirmation by the following day, so that treatment may then be started. Several blood cultures should be taken each day until the presence or absence of bacteremia is established.

It is best to make pour plates in addition to broth cultures. With the aid of the former, the density of the bacteremia can be determined and contaminants can be recognized. The cultures should be incubated

of using the terms acute and subacute. Under the heading of non-hemolytic streptococcic endocarditis, however, we shall describe the typical picture of what is often called subacute bacterial endocarditis.

SYMPTOMS AND SIGNS

If careful inquiry is made, a history can often be obtained of the removal of teeth or tonsils or of an upper respiratory infection a few days to a few weeks before the actual onset. Fatigue, lassitude, loss of appetite and weight, and transient pains in the muscles and joints are the complaints which frequently bring the patient to the physician. On the other hand, the first warning of the presence of the disease may be a sudden pain in the region of the spleen or kidney, a cerebral accident, or some other evidence of embolization.

Sweating is common, and chills may occur. There is irregular fever, in some cases only 1 or 2 degrees above normal and in other instances rising as high as 104° and 105° F. Sometimes the fever is intermittent in character, but more often it is remittent or irregular. It may disappear without specific treatment of the disease for days or weeks, only to return again later.

Cardiac Manifestations. Evidence of underlying rheumatic, congenital, or occasionally syphilitic heart disease is usually present. Vegetations occur most commonly on the mitral or aortic valve or on both. The pulmonary and tricuspid valves are less frequently involved. Usually the murmurs present are of a blowing quality and indistinguishable from those of the underlying disease, although careful examination of the patient from day to day often reveals a change in the quality or in the intensity of a murmur during the course of the disease. In rare instances, especially when the only valves affected are those on the right side of the heart, no murmurs will be heard during part or all of the course of the disease. Kelson[13] found heart murmurs in 99.2 per cent of 250 cases.

Embolic Manifestations. Portions of the vegetations may be dislodged from the valves from time to time, resulting in a variety of signs and symptoms depending upon where they lodge. Petechiae in the skin and mucous membranes are thought to be due to emboli. Kelson found them in 86.5 per cent of his cases. Petechiae are found especially in the palpebral conjunctivae, around the neck, shoulders, and arms, but they may be seen anywhere on the skin or mucous membranes or in the retina. They are irregular, nonelevated, red or purplish spots about 1.0 to 1.5 mm. in diameter. When they occur under a fingernail or toenail they look exactly like a splinter embedded there, hence the name "splinter hemorrhages."

Osler's nodes are another presumably embolic phenomenon. They are painful, slightly raised nodules, purplish red in color, sometimes with a white pinpoint center, occurring around the joints of the hands

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Infections characterized by petechial rashes which might be confused with bacterial endocarditis are meningococcemia meningococcic meningitis and typhus fever Other diseases which must be considered because long standing fever is characteristic include influenza tuberculosis undulant fever the lymphomas and other malignancies malaria localized deep-seated pyogenic infections and thyrotoxicosis Finally there are the endocarditides caused by other bacteria such as beta hemolytic streptococci pneumococci streptococci and less frequently other organisms The diagnosis may be suspected if there is a preceding or associated infection with one of these organisms but the blood culture must be depended upon to make the definite differentiation

PREVENTION

Transient bacteremia has been observed after the removal of teeth or tonsils and in patients with pyorrhea even after chewing or massage of the gums In view of these facts and since endocarditis has been found to follow closely upon tonsillectomy or the extraction of teeth it is highly desirable that an antibacterial agent be found which will prevent the bacteremia The value of the sulfonamides for this purpose is questionable inasmuch as several cases of endocarditis have developed in spite of sulfonamide prophylaxis

Penicillin because of its greater effect against nonhemolytic streptococci offers more promise We found that among sixty five patients who received penicillin before the extraction of teeth 14 per cent developed a transient bacteremia Among sixty five control patients who received no prophylaxis 34 per cent had micro-organisms in the blood In two of the control patients the bacteria remained in the blood as long as thirty minutes while none of the penicillin treated patients had positive blood cultures for this length of time

At the present time the actual value of penicillin in preventing endocarditis has not been established Until more evidence is forthcoming we suggest that all patients with abnormal or damaged heart valves be given 600 000 units of penicillin in oil and beeswax four hours before teeth are extracted If desired sulfadiazine or sulfamerazine may be given in addition beginning twenty four hours before extraction and continuing for the same length of time afterwards The same regimen should be followed for tonsillectomy and rectal operations This regimen should be carried out not only for patients with congenital rheumatic and syphilitic heart disease but also for the growing numbers of persons who have healed bacterial endocarditis

both aerobically and under increased carbon dioxide tension They should not be discarded as negative until they have been incubated for at least three weeks This is particularly true if the patient has already received penicillin since bacteria are likely to grow out slowly under these circumstances When valves on the left side of the heart are involved blood cultures should yield positive results If only the right side of the heart is affected a positive blood culture may be harder to obtain but even then repeated attempts should eventually be successful

Blood counts are not pathognomonic They usually show moderately severe or severe hypochromic anemia The leukocyte count is most often in the range from 10 000 to 16 000 per cu mm although it may be within normal limits Rarely is it over 16 000 There is usually a slight relative increase in the granulocytes and some shift to the left of the Schilling index

The *urine* usually contains albumin and casts as in most infectious diseases A more significant finding is the occurrence of microscopic quantities of red blood cells Gross hematuria and red blood cell casts are less frequently observed

Diagnosis

The presence of remittent intermittent or irregular fever along with heart murmurs and embolic manifestations should make the diagnosis almost certain When the embolic phenomena are absent the disease can only be suspected unless the character of the murmur changes under observation The recovery of alpha or gamma type streptococci by culturing the blood should establish the diagnosis when clinical evidences of the disease are present It must be remembered however that these organisms have occasionally been recovered from the blood of normal persons especially after tooth extraction or vigorous massage of the gums

Differential Diagnosis The diseases which should be considered in the differential diagnosis can be listed according to the manifestations of endocarditis with which they may be confused The joint manifestations and fever may resemble those present in acute rheumatic fever the acute phase of rheumatoid arthritis gonococcic arthritis or brucellosis In rheumatic fever petechiae and Osler s nodes do not occur characteristic electrocardiographic changes may be present the blood culture is negative and the fever should respond to salicylates In rheumatoid arthritis there is an absence of petechiae and of Osler s nodes and the blood culture is negative Gonococcic arthritis may present a definite problem especially if there is an associated endocarditis and bacteremia with petechiae A history of recent gonorrhea the presence of urethral or vaginal discharge or of bilateral conjunctivitis would be in favor of a gonococcal infection Absolute diagnosis

must rest upon the blood culture The diagnosis of brucellosis would be likely if there is a history of the ingestion of raw milk or of contact *with infected animals a positive blood culture agglutination test or* skin test

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Treatment

Penicillin Although the sulfonamides appear to have some effect upon the disease penicillin offers a much better chance of success Before the sulfonamide era only an occasional recovery occurred Kelson[13] reported that one of his 250 patients had apparently recovered When sulfonamides were employed they often sterilized the blood stream and caused temporary improvement but in most cases the organisms continued to multiply within the vegetations and only a relatively small proportion of the patients eventually recovered

When penicillin was first used in the treatment of bacterial endocarditis the doses were so small that at most only transient improvement was obtained To Loewe[16] goes the credit for demonstrating that with large doses of penicillin it was possible to abolish the infection completely Since then there have been hundreds of cases in which the disease has been arrested by treatment with penicillin Since some of these patients have remained free of infection for periods of three years or more we can now use the word cure in connection with the penicillin treatment This concept is corroborated by pathological evidence

Moore[17] has studied the valves of patients with endocarditis who died during a course of penicillin therapy and of other patients who had apparently recovered and who died of other causes In this way he was able to determine that the healing of vegetations took place in five stages as follows (1) the superficial layer of fibrin was replaced by fibrous tissue and at the same time fibrous tissue at the base of the vegetation extended so that the central necrotic core containing the great masses of bacteria was isolated (2) the layer of colonies was invaded and the bacteria were phagocytized (3) some bacterial colonies were calcified (4) hyalinization and calcification of the necrotic part of the vegetation took place next and (5) endothelial cells lined the spaces left by the destruction of bacterial colonies Moore estimated that this entire process may take from three to six months altogether

It is readily apparent that if penicillin therapy should be discontinued in any case before all the bacteria are killed and phagocytized they might again proliferate and in time the vegetation would be returned to its former state Since the bacteria would be contained in masses buried deep in the recesses of the vegetation there would be no clinical manifestations to indicate that they were still alive until some days or weeks had elapsed This is exactly the sequence of events which has been observed when relapse occurs in a patient with endocarditis after a short course of treatment with penicillin For this reason we have arbitrarily chosen eight weeks as the minimum period of penicillin therapy in bacterial endocarditis None of the fifteen patients whom we have treated for this period of time has experienced a relapse

According to the present state of knowledge the recovery rate among

all patients with endocarditis caused by alpha and gamma streptococci is about 70 per cent Among twenty six patients consecutively treated by us nineteen (or 73 per cent) have recovered As we learn more about the principles involved in penicillin therapy and improve our techniques accordingly the proportion of patients who recover will probably be increased still further

The prognosis is not influenced by any of the following factors the age of the patient the number and location of the affected valves the presence or absence of embolic manifestations or the duration of the illness before therapy Accordingly nothing should deter the physician from treating with penicillin any patient with streptococcic endocarditis no matter how hopeless the patient s condition may appear Others as well as we have been overjoyed to see patients recover who were apparently moribund when the first dose of penicillin was given

DETERMINATION OF THE SUSCEPTIBILITY OF THE INFECTING ORGANISMS Many strains of nonhemolytic streptococci are affected by low concentrations of penicillin approximately three-fourths of them being killed in vitro by concentrations of 0 03 units per cc The streptococci commonly found in the mouth usually fall within this sensitive group On the other hand inhibition of the growth of certain strains notably those classified as *Streptococcus faecalis* may require from 2 to 30 units of penicillin per cc or more Since the doses of penicillin ordinarily used for the treatment of endocarditis do not provide blood concentrations sufficiently high to inhibit all nonhemolytic streptococci the wisest course is to determine the sensitivity of the organism to penicillin before treatment is started Penicillin should then be given in amounts which will insure a concentration that remains consistently above four to eight times the sensitivity of the infecting strain (see p 78) If the patient s condition does not justify waiting until sensitivity tests can be completed the patient can be given penicillin while *the test is being performed and the dose can be changed if necessary* when the sensitivity is known

SUGGESTED REGIMEN FOR PENICILLIN TREATMENT When it is impossible to determine the sensitivity of the infecting organism or when it is desired to start therapy before the test is completed we feel that the patient should be given 50 000 units of penicillin every two hours intramuscularly or 300 000 units during each twenty four hour period by continuous intravenous or intramuscular infusion A favorable response is indicated by a fall in the temperature to essentially normal levels disappearance of toxicity and of positive blood cultures This usually takes place within two to seven days If the temperature remains normal and the blood cultures become sterile penicillin therapy may be discontinued at the end of eight weeks If the patient does not respond in this way the sensitivity of the causative organism should be determined if this has not already been done and the dose adjusted

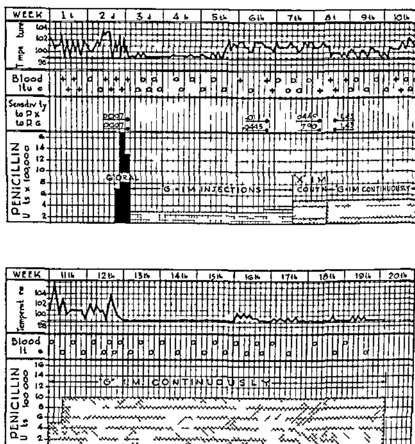


Fig 28 Temperature chart of a patient with bacterial endocarditis caused by *Streptococcus viridans* showing pronounced increase in resistance of the organisms during treatment

F J a Negro aged twenty two years had a questionable history of syphilis and no history of rheumatic fever Three weeks before admission he had headache followed by pain and stiffness in the cervical spine and swelling of both feet and ankles He was acutely ill on admission to the hospital with a temperature of 102 F a pulse rate of 112 and a blood pressure of 140 systolic and 60 diastolic There was a systolic thrill in the third and fourth interspaces to the left of the sternum and systolic and diastolic murmurs maximal in the same area and transmitted over the entire precordium The liver edge was 4 cm below the right costal margin The spleen was not felt A roentgenogram of the chest revealed slight enlargement of the left ventricle and of the pulmonary conus area and a moderate increase in the pulmonary vascular shadows

When six blood cultures, taken on different days had grown the *Streptococcus viridans* the patient was started on penicillin G by mouth For the first twenty four hours the dose was 100,000 units in amphojel every four hours and for the next twenty fours hours 200 000 units every four hours Since this did not seem to be influencing the course of the disease the dose was changed to 25 000 units of penicillin G intramuscularly every two hours. A test of the etiologic organism at this time for sensitivity to penicillin revealed that 0 0007 unit per ml of either the X or G fraction was sufficient to inhibit its growth

The temperature fell and the blood cultures became negative on the intermittent intramuscular injections but after a week fever and bacteremia reappeared The sensitivity of the organism cultured at this time had risen to 0 01 unit per ml in

accordingly (see p 78) When the dose has been established by determining the sensitivity of the organism whether from the beginning or at a later point in the course of treatment it should be continued at that level for the entire eight weeks of therapy unless something occurs which necessitates increasing it

Sometimes during the course of penicillin therapy or when the infection *is apparently completely controlled as judged by the absence of* fever and continued sterility of the blood cultures petechiae and other evidences of infarction will appear This is apparently due to the dislodging of emboli from the vegetations even though they are no longer infected When this complication occurs alone it need not be considered an indication for continuing penicillin therapy any longer or for starting it again if it has been discontinued

Patent Ductus Arteriosus Patients with endarteritis in a patent ductus arteriosus should be treated with penicillin in the same manner as if they had valvulitis After the infection has been cured studies can be made and a decision reached regarding the feasibility of ligation of the ductus If the operation is decided upon it can be performed when the patient s general condition is good

Complicating Factors in Therapy Congestive heart failure sometimes appears in patients under treatment with penicillin or after recovery from the infection One reason for this is that the valves may be sliced to pieces by the infection so that even if they heal under penicillin therapy they will remain incompetent and congestive heart failure will supervene Another reason is that the calcification of the valves which occurs as a part of the healing process[17] may produce stenosis of the affected valve and thus bring about congestive heart failure Two of our patients (8 per cent) died of congestive heart failure several months after they had recovered from the endocarditis Examination of the heart at autopsy confirmed the fact that the infection had been cured

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the ca e of penicillin X and 0 04 un t in the case of penicillin G Penicillin X wa tried in doses of 00 000 units a day by continuous intramuscular infu ion without success Positi e blood cultures continued to make th ir appearance and the sensitivity of the organism ached 0 04 unit per ml and 0 18 unit per ml for the X and G fract ons re pecti ely Owing to the scarcity of penicillin X at that time treatment was re um d with penicillin G in doses f 500 000 unit a day by continuous intramuscul r infu ion The sen iti ty of the organi m was again tested and found to be 1 4 units per ml for both the X and G fra t ons As a esult of this the dose was doubled After a few days on 1 000 000 units a day by int a muscular infu ion the pat ent impro ed con iderably the temperature fell and the blood culture became and re named sterile After nine weeks of this r g men the patient left the hospital against advice He was ex mined four m nths later and found to be free of sympt ms and of all evidence of infection

With the exception of the first few days when the patient was being t eated o ally the concentrations of penicillin in the blood were always higher than the amount of penicillin required to inhibit the growth of the organism in vitro In spite of this the inf ction remained active until a dose of 1 000 000 units a day was g en

Acute rheumatic fever has also been observed in patients who have recovered after treatment with penicillin This may in its turn produce congestive heart failure Pulmonary infarctions complicating heart failure may cause fever and thus make it difficult to determine whether an active infection is still present in the valves or not If fever and pulmonary infarctions are present and the blood cultures remain sterile further penicillin therapy is not indicated

When inadequate doses of penicillin are employed and sometimes when the doses are apparently high enough to insure that the infecting organism is being killed the resistance of the organism to penicillin increases Figure 28 illustrates such a case For this reason it is important to take blood cultures every day until the temperature is essentially normal and weekly thereafter throughout the period of treatment and for at least two weeks thereafter If the temperature rises or other complications appear blood cultures should be done more frequently If the blood culture again becomes positive the sensitivity of the organism should be tested immediately and the dose adjusted so as to secure minimal concentrations of penicillin at least eight times as great as the concentration which inhibits the growth of the organism

Treatment of a Relapse If the signs and symptoms of endocarditis return at any time after penicillin therapy has been discontinued the organism should again be obtained by culturing the blood its sensitivity should be determined anew and the dose adjusted accordingly In some instances relapses will respond to the same dosage of penicillin given during the first course but it is never wise to take a chance on this We believe that in the treatment of a relapse penicillin should be given for at least eight weeks

It is important to bear in mind that valves which have once been the site of an endocarditis may be infected later by another organism In fact the damage inflicted by the endocarditis and the changes incident to healing may predispose the valves even further to infection This is all the more reason for culturing the organism and determining its penicillin sensitivity in the event of a suspected relapse

Other Measures The patient should stay in bed until the temperature has been normal for a week unless pulmonary infarctions congestive heart failure or other complications necessitate bed rest for a longer period of time The diet should be high in protein and in calories especially if much loss of weight has occurred

In the past it was the custom to give repeated transfusions to correct the anemia We have found that these are now seldom necessary since the hemoglobin content increases progressively as the patient improves under penicillin therapy If he has a profound anemia when first seen it may be advisable to give one or two transfusions at the start of treatment

Urinary Infections Caused by Nonhemolytic Streptococci

Pyelitis and pyelonephritis are sometimes caused by nonhemolytic streptococci The treatment of these infections is considered on page 426 along with infections of the urinary tract by other bacteria

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10 Staphylococcic Infections

Staphylococci are gram positive cocci which usually occur in grape-like bunches less often in pairs or chains They are commonly found as parasites on the skin and mucous membranes of the respiratory tract Sometimes however virulent strains penetrate the barriers of these tissues. They then may cause any degree of infection from a small sharply circumscribed furuncle to a rapidly spreading overwhelming lethal systemic infection

In general the pathogenic staphylococci belong in the *Staphylococcus aureus group* (that is they produce golden pigment) are classified in Type A by the precipitin test and give a positive coagulase test Those strains not pathogenic are likely to produce no pigment (*Staphylococcus albus*) or yellow pigment (*Staphylococcus citreus*) to fall into Type B and to give a negative coagulase test This distinction is by no means rigid however since strains which are ordinarily non pathogenic may become so when the patient s resistance is lowered When they do cause disease it is likely to progress more slowly than infections caused by the more pathogenic types, although the eventual outcome may be none the less severe

Wherever the staphylococcic infection may be and however widely it may spread it will have one outstanding characteristic by destroying the tissues of the host in focal areas it will produce purulent abscesses. There may be only a single abscess or there may be several in the same area or in the same organ Even when the infection breaks into the general circulation unless death takes place within a day or so abscesses will form in various locations

Local and General Staphylococcic Infections

Localized Staphylococcic Infections

The chief portal through which staphylococci enter the body is the skin. They produce furuncles and carbuncles in areas of apparently normal skin and often cause inflammation of injured areas such as wounds burns and compound fractures Furuncles vary in size from a pinhead pustule to an abscess of several centimeters in diameter Carbuncles are large deep abscesses with several openings to the surface Whenever the staphylococcic lesion is large enough the regional lymph nodes enlarge become tender and may suppurate

The next largest group of infections caused by staphylococci are in the respiratory tract rhinitis sinusitis tracheobronchitis and pneu

monia Sometimes the inflammation extends to the middle ear and the mastoid cells Acute and often fulminating infections of the respiratory tract are frequent in infants and younger children While they may occur also in older children and adults the tendency in the latter age group is toward more chronic infections

Infections of the urinary tract are common Pyelitis is encountered often Pyelonephritis abscesses of the kidney usually multiple and perinephric abscess may also occur Staphylococci are the commonest agents causing osteomyelitis They are sometimes responsible for puerperal sepsis empyema arthritis meningitis endocarditis pericarditis and abscesses in other regions of the body

Generalized Staphylococcic Infection Bacteremia

The staphylococci in a local lesion may cause phlebitis of large veins or thrombophlebitis of smaller veins in the area surrounding the initial lesion Fragments of the thrombus are sometimes detached and swept through the lungs where septic infarcts are formed From these fresh emboli may tear away and travel to any part of the body to form single or multiple abscesses The kidneys are especially likely to be affected also the endocardium brain and spinal cord In all these cases staphylococci can usually be cultured from the blood during one period or throughout the course of the infection A constant staphylococcic bacteremia may occasionally occur without antecedent inflammation of the veins Whatever the events leading up to it persistent staphylococcic bacteremia is a serious and often fatal disease

Most patients with staphylococcic bacteremia are extremely toxic with a high irregular or remittent fever and a rapid pulse rate An initial chill or repeated rigors are often seen In an occasional patient there will be only low grade fever and few signs of toxicity The leukocyte count is usually moderately elevated with a shift to the left of the granulocytes Almost invariably a focus of infection in the skin respiratory tract urinary tract or elsewhere can readily be found The organisms are usually cultivated from the blood with ease

Lyons[11] believes that intravascular extension of a localized staphylococcic infection should be suspected when one of the following is present a leukocyte count of 15 000 or more a chill a sudden rise in temperature to 103° F or higher symptoms and signs of pulmonary infarction a palpably thrombosed vein or a positive blood culture

Complications and Associated Diseases

As already stated a staphylococcic infection in one part of the body is often followed by metastatic abscesses elsewhere Infections with access into the general circulation often metastasize to the lungs forming infarcts which break down into abscesses Infections in the lungs may

scatter abscesses through the general circulation which involve particularly the kidneys the central nervous system and the heart

A *staphylococcic infection anywhere in the body may occasionally* cause a typical scarlatiniform rash[13] This is due to a toxin produced by the staphylococci The rash resembles and runs the typical course of the rash of scarlet fever (see p 137)

Staphylococcic infections are often found in patients with diabetes mellitus The coexistence of these two diseases makes the prognosis *of each decidedly worse than if it were present alone* Consequently it is important that a history of previous diabetes be sought for and that the urine and if necessary the blood be examined for dextrose If diabetes is found it should be brought under control as rapidly as possible (usually this will require insulin) at the same time that specific treatment of the staphylococcic infection is being vigorously carried out

Staphylococcic bacteremia is frequently found in debilitating diseases and in the terminal phase of such diseases as leukemia thrombocytopenic purpura and carcinomatosis

Diagnosis

Local staphylococcic lesions are usually easy to recognize by the thick cream-colored pus which they contain When there is any question as to the etiology a smear of the pus stained by the Gram method will usually show the gram positive cocci in characteristic clusters Better still the organisms should be cultured

In bacteremia the organisms are easily cultured from the blood so easily in fact that a few staphylococci from the skin sometimes *contaminate otherwise sterile blood Consequently unless the physician* has corroborating evidence of a staphylococcic bacteremia it is well for him to insist upon two positive blood cultures before he makes a definite diagnosis The use of pour plates in addition to flask cultures helps to resolve this difficulty

Prognosis

Patients with localized staphylococcic infections usually recover if the lesion does not involve extensively a vital organ such as the kidneys or the brain In infants in the aged and in patients with complicating diseases such as diabetes or nephritis the illness often ends fatally even though it does not spread to other parts of the body

When staphylococci do enter the blood stream the prognosis is far graver As shown in Table 36 before the sulfonamides were available 72 per cent of bacteremic patients died When the sulfonamides were employed the case fatality rate dropped to 49 per cent With the use of penicillin only 21 per cent of the patients died Here again patients

in the youngest and oldest age groups had the poorest prognosis as did also those with serious complicating diseases

TABLE 36

CASE FATALITY RATE IN STAPHYLOCOCCIC BACTEREMIA ACCORDING TO TYPE OF TREATMENT

Type of Treatment	*No of Patients Treated*	*Died*	
		Number	*Per cent*
Presulfonamide era	823	591	72
Sulfonamides alone	164	80	49
Penicillin (with or without sulfonamides)	95	22	4

TREATMENT

Penicillin Most strains of staphylococci are sensitive to low or moderately high concentrations of penicillin About 90 per cent of the strains are inhibited by concentrations of penicillin ranging from 0 01 units to 0 35 units per cc The remainder are sensitive to concentrations up to 3 units per cc

Clinically the antibiotic has achieved notable success in staphylococcic infections Patients with milder infections such as subcutaneous abscess may be given intramuscular injections of 15 000 units every three hours or since they are most likely to be ambulatory 100 000 units by mouth every three hours or an injection of 300 000 units in beeswax and oil intramuscularly once a day When large abscesses or carbuncles are present or when the patient s general condition is not good the doses may be increased to between 25 000 and 100 000 units every two hours or 300 000 to 600 000 units in oil and beeswax every twelve hours Oral therapy should not be employed in these severer cases The duration of treatment depends upon the clinical response although it should not be less than four days in any event

Under such regimens most abscesses heal rapidly without requiring incision and surgical drainage Within forty eight hours after the first dose of penicillin pus is discharged spontaneously or resolution of the purulent contents takes place without evacuation Hamilton[8] noted that the furuncle or carbuncle sometimes became more swollen and painful and the patient more toxic within twenty four to thirty six hours after the initial injection of penicillin After this phenomenon rapid improvement began He attributed this sequence of events to the lysis of the staphylococci with consequent liberation of toxins If this interpretation is correct the reaction resembles the Herxheimer reaction which sometimes occurs in the treatment of syphilis (see p 86)

Multiple abscesses also heal well In severe cases where treatment has been delayed for several days it may be necessary to incise and drain the lesion surgically In such cases penicillin should be given also the first dose being administered three to six hours before the operation if possible

Abscesses containing pus can be aspirated by syringe and needle and 25 000 units of penicillin injected while the needle is kept *in situ* This may be repeated once or twice a day until the signs of active inflammation are gone

In severe staphylococcic infections where vital areas are involved or where bacteremia is present large doses of penicillin are needed From 25 000 to 100 000 units or more every two hours or 600 000 units in oil and beeswax intramuscularly every eight to twelve hours should be given If still larger doses are needed it is best to resort to continuous intramuscular or intravenous infusions By these methods from 500 000 to several million units a day may be given

The more severe and generalized the infection and the more pronounced the degree of toxemia the more careful the clinician should be to determine whether the organisms are causing infections in other places He should examine the urine repeatedly for evidences of pyelonephritis or renal abscesses and should be on the lookout for the development of pneumonia or pulmonary abscesses If the original focus is on the head sinus thrombosis and other intracranial involvement should be guarded against If none of these are found and the symptoms of fever and other evidences of toxicity subside it is best to continue penicillin therapy for several days to a week longer Relapses are particularly to be guarded against in staphylococcic infections since these organisms become penicillin resistant more readily than most bacteria

If the response to large doses of penicillin is not satisfactory the sensitivity of the staphylococcus to penicillin should be determined if at all possible and the doses adjusted accordingly At the same time a thorough search should be made for foci of infection particularly in the lungs, endocardium joints kidneys and meninges If foci are found they should be treated by the local administration of penicillin whenever this is feasible

Sulfonamides While the sulfonamides are partially effective against staphylococci the results they give are not nearly so satisfactory as those obtained with penicillin Although some investigators have recommended treatment with sulfonamides in addition to penicillin we have not seen better results when this combination was employed than when penicillin has been used alone If sulfonamides are used for any reason sulfathiazole is the drug of choice It should be given in full therapeutic doses (see p 44)

Other Specific Measures Before the advent of penicillin and

sulfonamides staphylococcic antitoxin staphylococcic antiserum and bacteriophage were used Although they were apparently helpful in some cases they are being discarded now that better therapeutic agents are available

Surgical Treatment This is needed especially where there is much devitalized tissue or debris in cases where systemically administered penicillin may not penetrate satisfactorily into the area of inflammation or where proper drainage will not occur without surgical intervention In all such cases penicillin should be given either locally or systemically or both

Staphylococcic Pneumonia

Staphylococci cause 1 to 8 5 per cent of all pneumonias in children Among adults these organisms are responsible for occasional cases In our series staphylococci caused 0 1 per cent of primary bacterial pneumonias During epidemics of influenza staphylococci may act as secondary invaders and cause many cases of pneumonia in patients of all age groups As stated before pneumonia is frequently secondary to staphylococcic infection elsewhere In such cases it occurs as a result of septic pulmonary infarcts Usually the general manifestations of sepsis are predominant and the signs of pneumonia not conspicuous Consequently the following remarks will apply particularly to the primary form of pneumonia

Staphylococcus aureus is the etiologic agent in most of the cases Among Blumenthal s[2] forty cases it was responsible for thirty five and *Staphylococcus albus* for the remainder Finland s[7] cases and ours in adults have all been due to the aureus variety

Symptoms and Signs

In adults the disease often follows symptoms of influenza malaise general aching and headache with or without upper respiratory symptoms Chills introduce the pneumonia only occasionally In most instances patients become progressively more toxic over the course of one to three days Cyanosis is present and often marked Rapid shallow sometimes irregular respirations are the rule The temperature is usually irregular with peaks of from 101° to 106° F The pulse is correspondingly irregular and rapid The sputum is usually purulent with streaks of blood or completely bloody When it is not bloody it usually varies from a dirty buff hue to salmon pink or light chocolate color Some patients complain of substernal tightness and a few experience pleural pain

In children two years of age or less there is almost always an upper respiratory infection The child develops a cough high fever fast pulse and respiratory rates and cyanosis These symptoms usually develop with alarming rapidity

Physical Examination

In adults and older children physical examination may reveal only sibilant and sonorous râles at first. Later crepitant rales appear over scattered areas indicating patches of consolidation. Various-sized areas of dullness and bronchial breathing may be mapped out. Sometimes the consolidation involves one or more complete lobes. In long standing cases signs of cavitation supervene. In young children more often than in adults the overwhelming intensity of the process causes consolidation of an entire lobe. Scattered areas of consolidation may occur however alone or in conjunction with complete lobar involvement. Furthermore empyema is found much more frequently in young children than in adults. In many patients with empyema there is a bronchopleural fistula with resulting pyopneumothorax.

Laboratory and X-Ray Examinations

The leukocyte count varies from patient to patient and at different times in the same patient anywhere from 3000 to 75 000 per cu mm. Only six of Blumenthal's[2] forty patients had leukocyte counts below 10 000 per cu mm. There is an increase in granulocytes and a shift to the left of the Schilling index. The sputum contains staphylococci in pure or nearly pure culture. In children in whom sputum is usually unobtainable the gastric contents may yield clumps of pus from which the organisms can be obtained. In other cases the diagnosis is made from the empyema fluid or from blood culture. These organisms usually have all the characteristics of virulence: they produce aureus pigment, are hemolytic and are coagulase-positive. Blood cultures were positive in four of Kanof's[9] twenty five cases of primary staphylococcic pneumonia and in all his twelve cases of the secondary type.

Roentgenograms in adults usually show scattered areas of infiltration in one or both lungs. Sometimes complete consolidation of one or more lobes is revealed. When the disease has lasted for several days one or many abscesses may be seen. Kanof[9] found that 80 per cent of children showed x ray signs characteristic of lobar pneumonia while the roentgenograms of the remainder showed bronchopneumonic infiltration. When there is consolidation of one lobe or of an entire lung there are often scattered patches of infiltration elsewhere.

Course and Complications

The disease in many patients is fulminating resulting in death within one to five days. Other patients may live from two weeks to a couple of months long enough to develop necrosis of the lung parenchyma with the formation of single or multiple abscess cavities. Still others may survive extensive lung involvement especially with the use of modern therapeutic agents. These patients will usually show a gradual decline in fever and toxicity. Several weeks may elapse before the

physical and x ray signs of pulmonary involvement clear up completely

Empyema is especially frequent in children under three years of age[4] Kanof[10] encountered it in 87 per cent of the primary cases and in 58 per cent of the secondary cases in children of all ages This complication usually makes its appearance earlier in staphylococcic than in pneumococcic pneumonia being present in most cases within the first week and occasionally as early as the second day Sometimes empyema occurs as a result of the rupture of a staphylococcic cavity into the pleura In such cases it may be detected by the fact that the patient takes a sudden turn for the worse with increased cyanosis pulse and respiratory rates and fever Usually a pyopneumothorax develops as a result of the connection of the cavity with a bronchus The prognosis is much worse than when air is not present and calls for immediate closed drainage with the insertion of a tube the free end of which is kept under water

Among adults empyema is frequent in patients who survive the first week or two of the disease The clinical characteristics are the same as those of empyema caused by the pneumococcus (see p 124)

Failure of the right side of the heart may occur in patients with extensive pulmonary involvement Metastatic staphylococcic abscesses may form in various parts of the body although they are not found so frequently as in other staphylococcic infections A scarlatiniform rash may appear in rare instances just as in other staphylococcic infections[12]

Diagnosis

This must rest on the culture of the sputum blood or empyema fluid although after influenza a pneumonia characterized by irregular fever rapid respirations pronounced cyanosis and buff salmon colored or frankly bloody sputum should make the physician suspect the staphylococcus as a cause The differential diagnosis includes the other bacterial pneumonias especially Friedlander bacillus pneumonia the virus and rickettsial pneumonias and also tuberculosis and pulmonary infarction (see p 110)

Prognosis

Before sulfonamides were used nearly all these patients died Finland[7] treated forty two patients with sulfonamides with thirteen fatalities Although experience with penicillin has not yet been extensive enough to produce figures of statistical significance the evidence is sufficient to show that a much smaller percentage of the patients will die when this drug is used

TREATMENT

This is the same as for any severe staphylococcic infection Penicillin should be given in doses of 50 000 to 200 000 units every two hours by intramuscular injection 300 000 to 600 000 units in oil and beeswax intramuscularly every twelve hours or by continuous intramuscular or intravenous infusion in amounts of 500 000 to 2 000 000 units during each twenty four hour period The patient should receive the general and symptomatic care prescribed for all patients with pneumonia (see p 115) Oxygen therapy should be started early (see p 17)

Treatment of Complications Penicillin should be employed in empyema in the same way as for the pneumococcic variety (see p 125) The reader is referred to Blumenthal's[2] article for a consideration of the surgical treatment of staphylococcic empyema

Osteomyelitis

Osteomyelitis denotes inflammation in a bone produced by a pyogenic organism Staphylococci are responsible for about 90 per cent of all cases In the most common form of the disease which is called acute hematogenous osteomyelitis the bacteria enter the body by way of the skin or the upper respiratory tract and are conveyed to the bone by way of the blood stream Occasionally osteomyelitis occurs as a result of spread of infection from adjacent structures and by direct implantation of bacteria within the bone as in a compound fracture The long bones are much more frequently involved than any others especially those in the lower extremities Trauma to the bone such as that which follows a fall or a wrench predisposes to localization in some cases Acute hematogenous osteomyelitis is a disease of childhood and is only rarely observed in adults The variety which is secondary to infected wounds may occur at any age

SYMPTOMS AND SIGNS

Localized pain in one part of the bone is the most important symptom Although a day or two of malaise and anorexia may sometimes precede the pain which occasionally starts as a feeling of stiffness the onset of the disease is usually abrupt with rather severe pain and sometimes a chill The pain is continuous and throbbing in nature and accompanied by toxicity and high fever Diarrhea vomiting or convulsions may occur A careful history will often elicit the fact that an infection of the skin or a sore throat preceded the illness by a week or more

In the first day or two of the disease the only sign which is present in most cases is tenderness over a limited area of the affected bone Passive motion of the neighboring joint does not cause pain provided that the procedure is carried out with care The patient shows evidence

of general toxemia with a temperature of 103° to 104° F and a correspondingly increased pulse rate

Within twelve to forty eight hours the infection usually reaches the periosteum From that time on swelling redness and edema develop the area of tenderness grows larger and the toxemia becomes worse Rupture of the periosteum may occur followed by a red fluctuant swelling Sometimes the nearby joint will be affected as indicated by swelling pain on motion and evidence of fluid within the joint cavity *If the blood supply of a portion of the bone is entirely cut off this* piece will become detached and act like a foreign body It is then called a sequestrum Sometimes there are metastases to the other bones where foci of osteomyelitis are likewise set up

If the condition becomes chronic localized abscesses sometimes form and discharge continuously through sinus tracts Another characteristic of the chronic stage is thickening of the cancellous portion of the bone with sclerosis of the medulla

Laboratory and X Ray Examinations

The leukocyte count is usually elevated to between 15 000 and 25 000 per cu mm In some cases it may exceed 30 000 The offending organism is often recovered from cultures of the blood as well as from cultures of the pus from abscesses or from the bone lesions at operation X rays will reveal no abnormalities in the affected bone for approximately the first week of the disease The first change is haziness in the affected area followed later by rarefaction due to bone destruction

Diagnosis

The sudden or gradual onset of pain in a long bone near a joint accompanied by signs of toxemia and localized tenderness in the affected bone is a picture not found in other diseases An elevated leukocyte count is confirmatory as are the characteristic roentgenographic changes The latter often appear late

Differential Diagnosis Osteomyelitis is most often confused with *diseases of the joints such as rheumatic fever and purulent arthritis* In osteomyelitis the pain and tenderness are not in the joint (except where a joint may later become secondarily involved) and the joints can be moved if movement is done carefully Furthermore patients with osteomyelitis are more toxic from the onset than most patients with arthritis

Cellulitis resembles osteomyelitis superficially but in cellulitis the involvement is more diffuse and the tenderness is much less pronounced and not so well localized Erythema and swelling appear with the toxemia of cellulitis whereas they are not seen until several days later in patients with osteomyelitis The differentiation from erysipelas is similarly made

Scurvy produces local but not constitutional signs and symptoms similar to those of osteomyelitis and furthermore has a characteristic *roentgenologic appearance*

PROGNOSIS

Crossan[5] reviewing the literature on osteomyelitis *from* 1923 *to* 1937 found that among 1504 cases reported there were 21 per cent deaths The prognosis has been improved somewhat by the use of the sulfonamides and is considerably better in patients who receive penicillin

TREATMENT

Local Measures The affected part should be placed at rest The decision as to the best method of accomplishing this whether by a simple pillow splint traction splint or cast depends upon the requirements of the particular patient and should be left to the surgeon Warm physiologic salt solution compresses may be applied to the affected area

Penicillin As soon as the diagnosis is made treatment with penicillin should be started Doses of 25 000 to 50 000 units every three hours or 300 000 units in oil and beeswax every twenty four hours are sometimes sufficient although larger doses 50 000 to 100 000 units by intramuscular injection every two hours 300 000 to 600 000 units in oil and beeswax intramuscularly every twelve hours or 500 000 to 2 000 000 units a day by continuous infusion will be needed in severely ill patients The following factors should be taken into consideration in determining the dosage the course of the temperature and pulse rate the severity of the local signs of infection the amount of pain the appetite the general appearance of the patient and the presence of infection elsewhere in the body The height of the leukocyte count will also be helpful.

The temperature does not drop abruptly In mild or moderately severe cases it falls and signs of toxicity disappear within seventy two hours after the first dose of penicillin is administered In these instances the temperature is completely normal within a week In severe cases defervescence may take several days longer The local signs of inflammation recede with the fever

The x ray changes[1] are slight in patients treated during the first three days of the disease consisting of small areas of periosteal reaction and decalcification of the cortex exhibiting little or no sequestration and seldom progressing after penicillin treatment is started The x rays of patients treated between four and seven days after the onset show similar although more extensive changes These often do not appear until a week or so after treatment is begun and progress gradually for the next month or two although they eventually dis-

appear When treatment with penicillin is not started for a week or more after the beginning of the disease destruction of bone is great and sequestration frequent The sequestrum usually absorbs spontaneously or remains in place to act as an autogenous bone graft in the rebuilding of the affected bone

Penicillin treatment will be needed in most cases for about three weeks In the cases where it has been employed the fatality rate has been reduced to the low figure of 1 or 2 per cent

Surgical Treatment Formerly there were two equally ardent and steadfastly opposed schools of thought as to whether or not operation was necessary in all cases Today penicillin is resolving the controversy since it brings about a cure in many cases when given systemically without the necessity of local treatment This is true for most patients whose treatment is started within a week of the onset In the occasional fulminating case with pronounced toxemia surgery is still needed and should be accompanied by preoperative and postoperative penicillin Surgical drainage is indicated if treatment is not started until after there is extensive damage to the bone with necrosis of the cortex and cavity formation It is likewise necessary when an abscess forms under the periosteum or when the infection enters the joint space

General Measures Pain may be severe at first and should be controlled by the appropriate drugs Since anemia is a frequent accompaniment of osteomyelitis repeated red blood cell counts or hemoglobin estimations should be made during its course Whole blood or suspensions of red blood cells should be given when moderate or severe anemia is found

Other Staphylococcic Infections

Meningitis

Infection of the meninges by staphylococci may follow otitis media sinusitis lesions of the skull or infections of the skin of the head Less often it is part of a generalized staphylococcic infection originating elsewhere Before the penicillin era this disease carried the poorest prognosis of any acute bacterial meningitis When penicillin is used about one-third of the patients recover although the death rate is still higher than in the meningitides caused by other organisms susceptible to this drug

Diagnosis If a patient with a local staphylococcic infection in the head or with a generalized staphylococcic infection develops positive Kernig or Babinski signs or stiffness of the neck or becomes delirious stuporous or comatose the possibility of meningitis should be entertained to the extent that a lumbar puncture should be performed immediately The cerebrospinal fluid should be examined according to the procedures outlined on page 208 When meningitis is present the cerebrospinal fluid will contain an increased number of leukocytes

usually between 100 and 1000 per cu mm with granulocytes predominating In all except the very mildest cases dextrose will be present in less than the normal concentration or will be absent altogether and the protein content will be increased Staphylococci are often seen on direct smear of the centrifuged sediment Otherwise they will be obtained by culture

Treatment Penicillin should be given intrathecally and systemically *For intrathecal administration 20 000 units should be dissolved in 10*

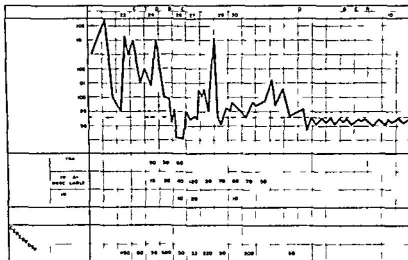


Fig 29 Temperature chart of a patient with staphylococcic bacteremia and meningitis treated with penicillin

K. B a man aged thirty-four developed swelling of the face from an alveolar abscess. On admission he was acutely ill with considerable edema and redness on the left side of the face and edema of the eyelids. The blood sugar was 400 mg per 100 cc *Staphylococcus aureus* was cultured from the blood and spinal fluid The patient was given penicillin by continuous intravenous and by intermittent intramuscular injections and also intrathecally After three days of this combined therapy the spinal fluid cultures became negative the leukocyte count declined somewhat, general toxicity disappeared and the local signs of inflammation receded The diabetes was brought under control with insulin Although irregular fever continued for a while it became normal after fourteen days of penicillin treatment *One week later the spinal fluid contained only 18 cells per cu mm, all lymphocytes.* Recovery was gradual but eventually complete

cc or less of physiologic salt solution and after the removal of a slightly larger amount of cerebrospinal fluid should be injected slowly preferably by gravity *At the same time 500 000 to 2 000 000 units a day* should be given by continuous intramuscular or intravenous infusion or by intermittent intramuscular injections at two hour intervals In infants the intrathecal and systemic doses may be halved Figure 29 shows the chart of a patient with staphylococcic meningitis who recovered after treatment with penicillin

Recovery should be judged by the fall in temperature and pulse rate by the disappearance of the signs of meningitis and of the organisms from the spinal fluid and the return of the spinal fluid dextrose to normal levels The leukocyte count may increase or remain constant for several days after penicillin therapy is started but will then decrease gradually as the patient improves Spinal fluid pleocytosis will remain however as long as penicillin is being given intrathecally

Endocarditis

This is the most dreaded complication of generalized staphylococcic infection It can be diagnosed with reasonable certainty in patients who have consistently positive blood cultures containing staphylococci and evidences of septic infarction either in the pulmonary or in the systemic circulation together with cardiac murmurs which appear or change in character during the period of observation Staphylococci almost always cause an acute endocarditis Vegetations appear upon normal as well as abnormal heart valves and the course of the disease is measured in days or weeks rather than in months Occasionally a less virulent staphylococcus such as an albus variety which is coagulase negative and not hemolytic will cause an endocarditis with a subacute course similar to that seen in *Streptococcus viridans* endocarditis Before the use of penicillin staphylococcic endocarditis was invariably fatal with its use we have obtained recoveries in six out of eleven patients[13]

Treatment is the same as for *Streptococcus viridans* endocarditis (see p 178) except that larger doses of penicillin are needed in most cases This is due to the acute nature of the endocarditis caused by staphylococci and the tendency of these organisms to produce abscesses

Arthritis

This condition may occur as a result of the extension of a neighboring osteomyelitis or it may arise during a generalized staphylococcic infection

Treatment Repeated intra articular injections of penicillin should be employed The joint cavity should first be aspirated as completely as possible by syringe then 50 000 units of penicillin dissolved in a volume of isotonic salt solution less than the amount of fluid removed should be injected The procedure should be repeated every forty eight hours until local symptoms have subsided fluid has disappeared from the joint and the general manifestations of the infection are gone If extra articular infection is present penicillin should be administered systemically also Recovery occurred in six of the seven patients treated by us[9] according to this method

Staphylococcic Food Poisoning

An important toxin produced by some staphylococci is enterotoxin so called because it produces symptoms in the gastrointestinal tract This disease comes to our attention most forcibly when epidemics occur in a group of people who have eaten the same food According to Dack[6] pies pastries (especially those filled with custard) pork and pork products milk and cheese are the foods most commonly implicated If staphylococci are introduced during the preparation of these foods and the latter are allowed to stand at room temperature for some hours the enterotoxin may be formed

Symptoms and Signs

Within two or three hours after the offending food is eaten (occasionally as soon as one or as late as six hours) severe nausea and vomiting occur Soon afterward abdominal cramps and diarrhea begin In mild cases there may be only nausea vomiting abdominal pain and diarrhea In severe cases vomitus or stools will be bloody and the gastrointestinal symptoms will be accompanied by headaches pain in the skeletal muscles and sweating In some instances there may be slight or moderately high fever in others the temperature will be subnormal and the blood pressure may fall Examination of the abdomen will reveal only moderate to severe tenderness throughout

Diagnosis

A history of vomiting or diarrhea or both of them coming on two or three hours after a meal with a story of similar symptoms in others who partook of the same food points strongly to staphylococcic intoxication Culturing staphylococci from the suspicious food will verify the diagnosis The presence of the enterotoxin can be determined by injecting a suspension of the food intraperitoneally into kittens Laboratory tests are not usually necessary however except as a public health measure

In the *differential diagnosis* many conditions must be considered In instances of intoxication from swallowing chemicals the symptoms usually appear sooner and a history of the ingestion of the poison can be obtained in most instances In botulism there is a history of eating improperly canned foods The symptoms may come on within a few hours or may be delayed for twenty four hours or more The most prominent symptoms are those indicating involvement of the central nervous system such as difficulty in swallowing diplopia and difficulty in speech and in respiration Symptoms due to a salmonella infection appear from four to seventy two hours (in most cases between twelve and twenty four hours) after the ingestion of the organisms and the symptoms of a shigella infection (bacillary dysentery) from

twelve hours to one week afterward The clinical characteristics may be similar to those found in staphylococcic infections although chills fever and prostration are more frequent in the salmonella and shigella infections (see Table 43 p 286) The *Streptococcus viridans* (alpha streptococcus) occasionally causes an infection with a clinical picture similar to the one encountered in staphylococcic food poisoning but the incubation period is usually longer (five to eighteen hours) and the symptoms are usually milder

Allergy to an ingested food is often responsible for severe nausea and vomiting and sometimes diarrhea The diagnosis usually can be made from the history since most patients will recall previous allergic episodes of the same or other kinds Furthermore other persons eating the food are not affected Other causes of gastrointestinal symptoms such as acute appendicitis intestinal obstruction gallbladder colic and so forth must be kept in mind

Treatment

There is no specific treatment The disease is self limited and practically never fatal It may indeed be over by the time the physician arrives If symptoms continue the bowel must be put at rest by the use of tincture of opium by mouth or morphine by injection if necessary If a considerable amount of fluid has been lost isotonic salt solution should be given parenterally

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we observed during an epidemic 164 (91 per cent) were caused by Group I two by Group II and fourteen by Group II alpha meningococci

Meningococcic Meningitis

Meningococci are present in the pharynx of normal subjects especially during epidemics Most of these individuals remain healthy but in some the organisms reach the meninges and produce the disease While it is possible for them to reach the meninges directly through the cribiform plate of the ethmoid *it is unlikely that this occurs often,* if at all In view of the fact that bacteremia is present in a large number of patients with meningitis and that the organisms are often found in the blood before there are evidences of meningitis the most likely route of invasion is from the pharynx to the blood stream and thence to the meninges This is of more than academic importance since an alert physician can often make the diagnosis of meningococcic infection before the organisms localize in the meninges As will be seen later treatment during this stage is very successful

SYMPTOMS AND SIGNS

The incubation period is often short—one to four days in most instances—but may be prolonged for a week or more when a patient becomes a carrier for a while and then develops meningitis later The onset was sudden in over half of our cases beginning with a chill or chilly sensations headache stiffness of the neck vomiting or any combination of these symptoms These various symptoms usually appeared within one or two hours of each other We have not seen a fainting attack at the onset but this phenomenon has been reported

In some patients the disease begins insidiously with a mild headache malaise general aching and a low grade fever for one to several days before definite symptoms or signs of meningitis appear

As shown in Table 37 the classic triad of stiffness of the neck headache and vomiting were the most frequent symptoms in 200 patients whom we observed The characteristics of these symptoms will be considered in more detail

The degree of nuchal rigidity varies considerably from patient to patient Some patients experience only slight pain when the head is brought forward while in others the neck cannot be pushed forward no matter how hard the examiner tries and all attempts to do so cause considerable pain In young children especially in infants the entire body may be arched backward by the pull of strong back muscles *This condition is called opisthotonus Toomey*[16] *has outlined the char*acteristics of stiffness of the neck due to meningitis and the pathological conditions which may simulate it Nuchal rigidity due to meningeal irritation usually occurs only with forward movement of the neck while lateral movement is possible In most instances it is accompanied

11 Meningococcic Infections

The *Neisseriae* are gram negative coffee bean shaped diplococci The two species which are important as far as human infections are concerned are *Neisseria gonorrheae* (gonococcus) and *Neisseria intra cellularis* (meningococcus) While these two organisms are usually thought of as being quite distinct from each other because the former usually causes an infection of the urinary and reproductive organs and the latter of the meninges they are actually closely related morphologically culturally and in their capacity to produce disease in humans Most of the sites frequently invaded by one organism are also susceptible to invasion by the other The meningococcus usually enters the body by way of the pharyngeal mucous membranes producing first bacteremia and then meningitis The gonococcus usually enters the body through the mucous membranes of the genitourinary tract and causes primary infection of the related organs On the other hand either organism may cause a primary conjunctivitis Either organism may enter the blood stream from the original site of entry and localize in the joints endocardium and conjunctivae and in other structures Furthermore the gonococcus may occasionally cause meningitis and the meningococcus may localize in the genitourinary organs

These facts are of importance to the clinician first because he can remember all the varied clinical manifestations of infection by each coccus better by grouping the two together and second because he must realize that he cannot depend upon clinical manifestations and morphologic appearance to tell him with certainty which organism he is dealing with in a given case For this he must depend upon fermentation reactions or serological differentiation

Meningococcic Infections

Meningococci are classified today into Groups I and II Group I includes the Types I and III of the old classification of Gordon and Murray and Group II includes Types II and IV of that classification A further refinement of the present method is to split off certain organisms from Group II and call them Group II alpha Rabbit serum is available for the typing of Group I and II alpha organisms These serums cause capsular swelling when brought in contact with a meningococcus of the same group Group I strains greatly predominate during an epidemic while in interepidemic periods the proportion of Group II strains increases somewhat Among 180 typed cases which

and often vary from day to day Deep tendon reflexes may be normal in intensity hyperactive or hypoactive Ankle clonus is observed in some patients The Babinski reflex is occasionally positive while absence of the cremasteric or abdominal reflex is rarely observed The pupils are usually normal in size and react properly to light and on accommodation but they may be contracted may be fixed without response to stimuli or may be unequal Nystagmus is a rare sign and indicates a grave prognosis *Disturbances of the cranial and peripheral nerves* will be discussed under complications



Fig 30 Purpuric rash of meningococcic meningitis. (Courtesy of Eli Lilly and Company)

Rash A characteristic feature of meningococcic meningitis from which one of its names spotted fever is derived is the cutaneous eruption We observed it in slightly over half (103) of our patients In almost all instances the rash is composed of petechiae which vary in size from pinpoint to 1 cm in diameter and in numbers from two or three to hundreds They are most often present on the trunk and upper extremities next most prevalent on the lower extremities and least often observed on the face Accompanying petechiae often appear in the mucous membranes of the mouth and conjunctiva and in the retina Six of our patients had a rash composed of pink macules and flat maculopapules up to 2 cm in diameter Another type of rash

by other neurological signs such as positive Kernig's and Brudzinski's signs opisthotonus and pain along the back Stiffness of the neck may be absent in infants in patients with extreme toxicity who die within a few hours after the onset of the disease and in those who have been ill a long time and who are examined just before death

TABLE 37

FREQUENT SYMPTOMS AND SIGNS IN 200 PATIENTS WITH MENINGOCOCCIC MENINGITIS

Symptoms and Signs		*Number of Patients*
Stiff neck		176
Headache		155
Vomiting		112
Upper respiratory infection		51
Chill		46
Stupor coma and/or delirium		118
Positive Kernig sign		114
Rash		103
Petechial	94	
Maculopapular	6	
Purpuric	3	
Positive Brudzinski sign		76

The headache may be of no more than moderate severity but is more often intense and practically unbearable One characteristic which helps to distinguish it from headaches due to other causes is the fact that it is confined to the occipital region or originates there

Vomiting is usually associated with nausea is sometimes projectile in type and is repeated many times

Convulsions are observed fairly often in children and occasionally in adults Abdominal pain is sometimes complained of and may be accompanied by so much muscular rigidity as to simulate appendicitis Other symptoms occasionally encountered are hematemesis diarrhea diplopia and pains in the joints

Sooner or later in the course of meningococcic meningitis the patients become stuporous or comatose or experience periods of coma alternating with periods of delirium We observed one or more of these conditions in 118 out of 200 patients Sometimes the change in the mental state is dramatically *sudden Within a few hours a perfectly* healthy individual may become comatose or wildly delirious As will be shown in the section on prognosis such an eventuality is greatly to be feared

Neurological Signs The neurological signs vary enormously from patient to patient Some patients with a mild form of the disease may exhibit no abnormal neurological signs at all or at most only slight limitation in the free movement of the neck As stated before 176 of the 200 patients observed by us had some degree of nuchal rigidity Positive Kernig and Brudzinski signs were next in frequency being present in 114 and 76 patients respectively

Other abnormal neurological signs are less frequent in meningitis

Fulminating Infections In some patients meningococci may *produce a disease of dramatic swiftness and severity* Victims of this bacterial lightning may be stricken suddenly at their work or play and be dead within a few hours A particularly fulminating form of meningococcic disease results in the *Waterhouse Friderichsen syndrome* Whether the patient has an upper respiratory infection at the start or not he suddenly becomes extremely sick with a high temperature (104° to 107 F) Chills convulsions and vomiting may occur as in other forms of meningococcic infections The distinguishing characteristics however are prostration rapidly developing extensive petechial or purpuric rash dyspnea cyanosis leukocytosis and signs of peripheral circulatory collapse such as feeble pulse low blood pressure cold damp skin and rales in the lung bases Oliguria or anuria supervenes At times edema develops also Consciousness is often retained up to a few hours before death when coma or delirium may come on This syndrome occurs especially in children although it may be seen at any age It is observed particularly during epidemics of meningococcic meningitis Fortunately it is not frequent Among 300 patients with meningococcic infections we encountered only four with the Waterhouse-Friderichsen syndrome Meningitis was present in two of these patients while the other two had meningococcemia alone Three of the four died including the two with meningitis

At the postmortem examination large numbers of meningococci are found within the capillaries They apparently damage the walls of these vessels so as to produce extensive hemorrhages which are especially prevalent in the skin and in the adrenal glands Although hemorrhages in the latter are present in nearly every case adrenal damage does not seem to be necessary in order to produce the typical clinical picture It is likely that severe injury to capillaries all through the body is sufficient to cause the syndrome and that the destruction of suprarenal tissue merely makes the matter worse by lowering the blood pressure further aggravating the collapse of the peripheral circulation and disorganizing the fluid and salt balance These factors will be considered more extensively in relation to the treatment of the condition

Banks[1] has described another fulminating form of meningococcic meningitis in which encephalitic features predominate with severe headache and rapid development of coma Pathological changes are found in the brain substance at autopsy

Laboratory Examinations

The Cerebrospinal Fluid Every patient suspected of having meningitis should have a spinal puncture performed immediately It is impossible to overemphasize the importance of obtaining cerebrospinal fluid promptly and of examining it intensively The procedure should

which we observed three times was a purpuric rash (Fig 30) This type is found in fulminating cases The petechial and purpuric spots remain unchanged for two or three days and then become brown and fade gradually over the course of one or two more days Maculopapular lesions ordinarily disappear within twenty four to forty-eight hours although occasionally they may become hemorrhagic first In a few patients we have observed a generalized erythematous blush which was present on admission to the hospital and disappeared shortly thereafter to be followed within the next few hours by the characteristic petechial rash

Another skin affection is herpes simplex around the lips Less frequently herpes zoster is seen

Fever The temperature follows no characteristic course Some patients will have only one or two degrees of fever while the temperature in others will range as high as 104° or 105° F and occasionally higher The temperature curve is irregular varying as much as two to three degrees during a twenty four hour period sometimes reaching normal and rising again Before sulfonamides were in use the temperature in most patients who recovered remained elevated for five to six days before descending by lysis In some instances the disease was abortive and lasted no more than twenty four or forty eight hours altogether In other cases it extended over a period of two weeks or more usually as a result of complications

The Respiratory System In most patients the respirations are regular and not remarkable and the rate is increased slightly if at all Breathing may be stertorous in comatose patients A few patients will exhibit the Cheyne Stokes type and a rare one the Biot type of respiration Cyanosis appears a few hours before death in many fatal cases and occasionally earlier than this

During the acute stage of the disease basilar rales are frequently heard and the presence of bronchopneumonia is sometimes detected by x ray examination Whether this represents a meningococcic infection of the lungs or merely a mixed bacterial infection of the kind found in many infectious diseases is an unsettled question

Circulatory System The pulse is elevated in proportion to the temperature although it may be slowed in patients with increased intracranial pressure The blood pressure is usually normal and may be lowered when a shocklike state is present A soft blowing systolic murmur may be heard during the disease in many patients Myocarditis has been detected by electrocardiographic changes in patients with severe infections

Other Features Occasionally signs indicative of increased intracranial pressure may be present These are bulging of the fontanelles in infants and papilledema at any age Incontinence of urine and feces will occur in severely ill patients

spinal fluid of the normal person no more than 10 lymphocytes per *cu mm should be present dextrose should be between 50 and 80* mg per 100 cc proteins between 15 and 40 mg and chlorides between 720 and 750 mg per 100 cc

In meningococcic meningitis the leukocyte count is almost always between 500 and 50 000 per cu mm and usually between 2000 and 30 000 We have obtained leukocyte counts as low as 30 per cu mm but this has been early in the disease presumably in the transition period between meningococcemia and meningitis The highest leukocyte count we have seen was 80 000 per cc The fluid is turbid in nearly every case of meningococcic meningitis since 200 or more polymorphonuclears per cu mm will produce turbidity In rare instances the fluid is xanthochromic The dextrose content is decreased in proportion to the number of meningococci present A mild infection with few organisms will cause no reduction at all while in severe infections the dextrose will be considerably diminished in amount or absent altogether Intravenous glucose should not be given before a diagnostic lumbar puncture since an increased level of dextrose in the blood will be accompanied by an increase in cerebrospinal fluid dextrose If dextrose has already been administered intravenously a specimen of blood should be examined for the dextrose content along with the spinal fluid The protein content is increased above and the chloride content decreased below the normal values

3 Five cubic centimeters or less should be taken for bacteriologic study Part should be inoculated into appropriate media as soon as the fluid reaches the laboratory and incubated promptly The remainder should be centrifuged and from the sediment two smears made one to be stained by Gram s method and one with methylene blue The latter is superior for determining the morphology of the organisms The proportion of polymorphonuclear cells in the stained smears should be noted In meningococcic meningitis these are the predominant cells If biscuit shaped gram negative diplococci are seen they should be typed directly by the *quellung* method with the use of Group I and Group II alpha rabbit antiserums In 91 per cent of 163 typed cases we were able to obtain the group directly from the spinal fluid by this method In the other 9 per cent the group was obtained only after *culture*

The Blood *The blood of every patient should be cultured before* treatment is started We obtained positive blood cultures in 26 per cent of our patients Meningococci can sometimes be obtained from the skin lesions Among eighteen patients with purpuric rashes McLean[11] was able to obtain the organisms in fifteen His technique was to pick a large lesion cleanse the skin over it with alcohol and allow it to dry Then a stab wound was made with a Hagedorn needle The extravasated blood and tissue juices were smeared on a slide which

never be harmful if strict attention is paid to asepsis a small gauge needle is used and the fluid allowed to escape slowly drop by drop so as to prevent too rapid decompression Even in patients who had bacteremia and no meningitis Pray[13] found that spinal punctures did not produce meningitis Our own experience has been in conformity with this

Local anesthetics other than procaine should be used since the latter neutralizes the activity of the sulfonamides and also gives the same color reaction thus producing falsely high figures in the quantitative determinations of the sulfonamide content of any fluid contaminated by it After the cerebrospinal fluid pressure has been determined the procedure outlined in Figure 31 should be carried out

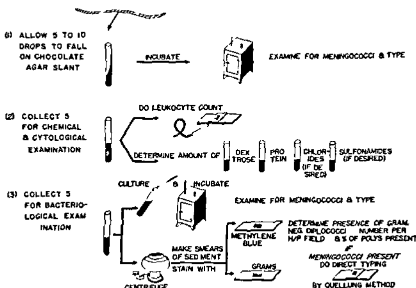


Fig 31 Examination of cerebrospinal fluid in meningitis

1 Five to 10 drops of the fluid should be allowed to drip directly onto a chocolate agar slant to be incubated in a candle jar or by some other method designed to increase the amount of carbon dioxide in the atmosphere In addition if it is possible the fluid should be collected directly into a tube of enriched broth such as tryptose phosphate broth or broth containing blood serum or ascitic fluid This should be held at room temperature or placed in an incubator as soon as possible since meningococci are easily killed by refrigeration

2 Five cubic centimeters (less in young children or infants) should be obtained for a leukocyte count and a determination of the dextrose and protein content Examination may be done on this fluid for sulfonamides if they have been administered and for chlorides if desired The latter are decreased in the bacterial meningitides In the cerebro-

was dried stained by Gram's method and examined A still higher percentage of positive results might have been obtained by cultivation

In 88 per cent of our patients the leukocyte count on admission to the hospital was between 12 000 and 15 000 the average count being

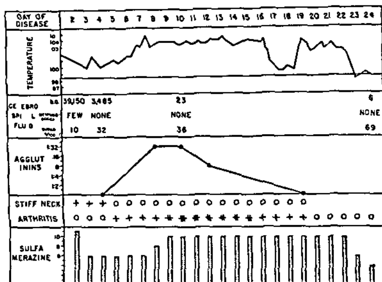


Fig 33 Temperature chart of a patient with moderately severe meningitis complicated by a severe attack of arthritis and partial facial paralysis

I A a girl aged seventeen years on admission had petechial and purpuric spots *all over her body and exhibited Cheyne-Stokes respiration* and slight rigidity of the neck The cerebrospinal fluid was under increased pressure contained 39 000 polymorphonuclear leukocytes per cu mm and less than 10 gm of dextrose per 100 cc A few meningococci were seen on smear and found to be Group I on direct typing Six gm of sulfamerazine were given immediately followed by 1 gm every four hours The day after treatment was begun the neck was still stiff and herpetic sores had appeared around the lips Lumbar puncture revealed 318 leukocytes per cu mm no meningococci and 32 mg of dextrose per cu mm On the fifth day of the disease arthritis of the wrist and right facial weakness *developed* Later the elbows and one knee also became painfully swollen and tender The temperature which fell slightly during the third and fourth days of the disease rose to levels of 104 and 105 F *while the arthritis was at its height It fell nearly* to normal on the seventeenth day of the disease and then rose and remained elevated from the nineteenth to the twenty third days This latter elevation was demonstrated to *be drug fever* when it disappeared on cessation of sulfamerazine therapy and reappeared when a second course of sulfamerazine was given A lumbar puncture done on the twenty fourth day of the disease revealed only six lymphocytes per cu mm no meningococci and dextrose within normal limits The agglutinins rose to 1 32 on the eighth day of the disease and reached normal on or before the eighteenth day

18 000 In a few patients whose leukocyte counts were below 12 000 the disease was mild and even these patients had leukocyte counts within the upper limits of normal the lowest being 9600 per cu mm

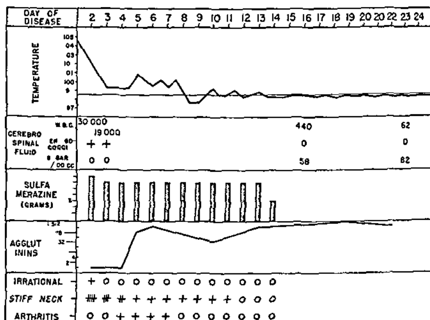


Fig 32 Temperature chart of a patient with moderately severe meningitis and arthritis treated with sulfamerazine

W C a Negro aged eighteen years on admission was irrational and had a temperature of 104 6 F a completely rigid neck a positive Kernig sign and numerous *petechiae all over his body The spinal fluid was under increased pressure* was cloudy and slightly xanthochromic and contained 30 000 leukocytes per cu mm nearly all of which were polymorphonuclears No dextrose could be detected Six gm of sodium sulfamerazine were given intravenously after the first samples of blood and cerebrospinal fluid had been taken followed by 1 gm of sulfamerazine every four hours by stomach tube By the following morning the patient was rational and much less toxic and his neck was slightly less rigid Sulfamerazine was given orally from that time on The cultures of the blood and cerebrospinal fluid taken on the previous day now yielded Group I meningococci A second lumbar puncture revealed 19 000 leukocytes per cu mm and the absence of dextrose Meningococci were cultured from this fluid also On the fourth day of the disease swelling and tenderness of the right elbow appeared and the temperature rose slightly but the neck was becoming less stiff by that time and the patient was mentally clear and alert Since the meningitis was considered to be improving and arthritis was apparently the cause of the slight fever no further lumbar punctures were done at this time The arthritis lasted only four days altogether Nuchal rigidity disappeared by the twelfth day and the sulfamerazine was discontinued on the fourteenth day Another lumbar puncture was done on the sixteenth day which revealed 440 leukocytes per cu mm (about 50 per cent of which were polymorphonuclears) and dextrose within normal limits No meningococci were obtained on culture The cerebrospinal fluid contained sixty two leukocytes (mostly lymphocytes) per cu mm on the twenty third day and fifty-one leukocytes on the thirtieth day Since this leukocyte count was still above the arbitrary level of thirty per cu mm which we require for discharge the patient was kept in the hospital and another lumbar puncture done on the thirty ninth day When this revealed only even lymphocytes per cu mm the patient was discharged The patient's agglutinin titer for Group I meningococci rose from 0 on the second day of the disease to 1 128 on the fifth day later rising as high as 1 512

not be severe enough to be accompanied by visual disturbances Paralysis of the oculomotor nerve is frequently seen causing diplopia outward deviation of the eyeball and ptosis It is usually unilateral as it was in all nine of our cases Abducens nerve paralysis is also common is also unilateral in most instances and also causes diplopia Here the eyeball is turned in and will not move outward beyond the midline The facial nerve may be affected on one or both sides Paralysis results in the loss of movement of the facial muscles on the affected side Hearing may be affected in meningococcic meningitis either as a result of otitis media or of injury to the auditory nerve The latter is the most frequent cause of deafness and is usually associated with disturbances of the cochlear portion of the acoustic nerve Involvement of the other cranial nerves is rare and is usually unilateral when it occurs

Two of our patients developed a monoplegia in one case affecting an upper and in the other a lower extremity Hemiplegias are more frequently seen although none were observed in our series Paraplegias and lesions of peripheral nerves are rare

The prognosis of neurologic complications varies considerably Many of the patients with paralyses of the third sixth or seventh nerves recovered by the time the cerebrospinal fluid had returned to normal In others completely normal function was not restored for weeks or months One of our patients who was afflicted with paralyses of the third sixth seventh and eleventh nerves achieved complete recovery eighteen months after the attack of meningitis The neurologic lesions cleared up completely in all our patients with the exception of eighth nerve deafness in two It has been the general experience that when this nerve is affected there is less chance of recovery than in the case of the other nerves Degen[8] in a follow up study of 986 recovered patients found twenty seven with total and six with partial deafness Farmer[6] analyzing approximately 300 cases of meningococcic meningitis encountered five patients with deafness Two had minimal recovery of hearing and three had none He stresses the fact that in children under eight years of age complete deafness usually results in deaf mutism

Among the complications elsewhere than in the nervous system arthritis and tenosynovitis were the most frequent being present in fifteen of our 200 patients. In two of these the arthritis was purulent and involved only one joint The other patients had varying degrees of pain tenderness and swelling usually in several joints The arthritis often migrated from one joint to another All our patients recovered without residua These findings may be compared with the 12 per cent incidence of arthritis found by Herrick[8] He divided his cases into two groups Type A twelve cases exhibiting an acute polyarthritis which did not appear later than the third day of the disease and was

Specific antibodies develop in the blood of patients during the course of meningococcic infections The most reliable test for routine use is the determination of the agglutinins We[5] have shown that these are elevated in most cases from the fifth to the twentieth day of the disease after which they fall rapidly to zero The agglutinin test can be used as an aid in the diagnosis of meningococcic infections when the organisms cannot be obtained on smear or by culture Figures 32 and 33 portray characteristic curves of agglutinin titers in two patients with meningococcic meningitis

The urine shows the changes found in most febrile diseases containing a small amount of albumin and a few casts Ferguson[7] found spontaneous glycosuria in over one third of his cases of meningococcic meningitis accompanied in many instances by ketosis hyperglycemia and diminished tolerance to sugar Glycosuria was transient in all cases

Complications

The complications may be divided into two groups depending upon whether they affect the nervous system or other parts of the body Table 38 lists the complications which we have observed in 200 cases Thirty seven patients exhibited forty four different neurologic complications Paralyses of cranial nerves occurred as follows in descending

TABLE 38

Complications in 200 Patients with Meningococcic Meningitis

		Number of Patients
Paralyses of Cranial Nerves		42
II Optic	1	
III Oculomotor	9	
VI Abducens	8	
VII Facial	14	
VIII Acoustic	8	
XI Accessory	1	
XII Hypoglossal	1	
Monoplegia		2
Of upper extremity	1	
Of lower extremity	1	
Arthritis and tenosynovitis		15
Conjunctivitis and ophthalmitis		9
Pneumonia		7
Waterhouse Friderichsen syndrome		1
Lung abscess		1
Otitis media		1
Thrombosis of femoral vein		1

order of frequency facial oculomotor abducens acoustic optic spinal accessory and hypoglossal Paralyses of other cranial nerves have been observed in rare instances

Optic neuritis is infrequent and when it occurs usually results in narrowing of the visual fields although complete blindness can occur The optic nerve may also be affected in meningitis by choking of the disk as a result of increased intracranial pressure This may or may

2 Exposure to cold or keeping in a peculiar position
3 Enlarged cervical lymph nodes
4 Neuritis of the occipital nerve
Pharyngeal abscess and Ludwig's angina
6 Osteomyelitis of the skull or vertebrae
Dislocation of the cervical bones
8 Congenital torticollis
9 Arthritis of the cervical spine
10 Injury to the vertebral ligaments

With the exception of meningismus these conditions can almost always be ruled out by a case history and examination of the areas involved If any doubt remains a lumbar puncture should be done

Diseases with a petechial or purpuric rash similar to that of meningococcic meningitis are typhus and Rocky Mountain spotted fevers occasionally typhoid fever purpura hemorrhagica drug rashes bacterial endocarditis and bacteremia caused by streptococci and other organisms The rash of measles may occasionally simulate the early maculopapular rash of meningitis but *the individual lesions are less* uniform and more numerous the face is affected more often and there is more confluence than in meningococcic infections

When joint symptoms predominate the disease must be differentiated from acute rheumatoid arthritis gonococcic arthritis and rheumatic fever

Other diseases of the nervous system which may be confused with meningococcic meningitis are the other bacterial meningitides virus *infections syphilis of the central nervous system* tetanus and *meningeal* irritation resulting from an abscess or an infarct in the substance of the brain or spinal cord A definite diagnosis is made by bacteriologic study of the blood and cerebrospinal fluid In tuberculous meningitis although the dextrose content is often lowered the predominant cells are the lymphocytes which seldom number more than 1000 per cu mm The presence of tuberculosis elsewhere the absence of any great degree of leukocytosis in the blood the absence of meningococci and the detection of tubercle bacilli in the stained sediment or concentrate of the cerebrospinal fluid will clinch the diagnosis

Virus infections of the central nervous system which may be confused with meningococcic meningitis are anterior poliomyelitis encephalitis mumps meningitis and meningoencephalitis benign lymphocytic *choriomeningitis and others which are less frequently encountered In* these and in syphilis of the central nervous system the cerebrospinal fluid contains less than 1000 or at most 2000 leukocytes per cu mm The cells are almost always lymphocytes except in early cases of poliomyelitis where the percentage of polymorphonuclears may be 80 or more The diagnosis of this disease must be made by the presence of paralysis and absence of bacteria in the blood and cerebrospinal fluid

Tetanus may be differentiated by the history and presence of a

transitory and Type B sixteen cases, with onset about the fifth day characterized by considerable swelling out of proportion to the amount of redness, pain tenderness and limitation of motion and usually affecting only one joint Recovery was complete in all except one patient

Conjunctivitis alone or accompanied by infection of other structures of the eye was present in nine of our patients all of whom recovered completely Pneumonia was present in seven patients We encountered lung abscess otitis media and thrombosis of a femoral vein each in one patient The Waterhouse-Friderichsen syndrome has been discussed on page 207

Other complications which have been reported in meningococcic meningitis are gangrene of the fingers or toes endocarditis pericarditis epididymitis orchitis pleurisy parotitis and peritonitis Smithburn[14] observed nephritis in 30 per cent of 114 cases When this condition occurs as a complication of meningococcic meningitis the pathology is usually confined to the tubules and permanent damage to the kidneys is rare

In the presulfonamide days blocking of the foramina through which the cerebrospinal fluid circulates or in the spinal subarachnoid space followed by internal hydrocephalus was a common and serious complication which occurred especially in infants Since the advent of chemotherapy it is fortunately rarely encountered

DIAGNOSIS

The patient who has intense headache stiffness of the neck and vomiting seldom presents any problem in diagnosis The cases of meningitis which may be easily overlooked are those in which there are general symptoms such as chills or chilliness aching and malaise joint pains or in infants irritability restlessness or drowsiness Likewise a patient who is comatose when first seen may be mistakenly considered to be in an alcoholic or diabetic coma There is only one sure way to avoid overlooking meningitis A neurological examination should be done a thorough search should be made for a rash and a lumbar puncture should be performed whenever there is any suspicion that meningitis may be present If the fluid is turbid or if the number of leukocytes is increased the procedure outlined on page 208 and in Figure 28 should be carried out If in addition a sample of blood is cultured the meningococci will be isolated sooner in some cases

Differential Diagnosis Toomey[16] states that the pathological conditions other than meningitis which can cause stiffness of the neck are

1 Other infectious diseases such as pneumonia pyelitis typhoid and salmonella fevers. The condition which occurs in these diseases is called meningismus and is characterized by the presence of the neurological signs of meningitis accompanied by no pathological changes in the cerebrospinal fluid or at most by a slight increase in lymphocytes

A third factor in prognosis is the number of meningococci seen in the smear of the centrifuged sediment from the initial spinal fluid specimen The death rate was considerably higher in patients showing many organisms in this specimen (more than one per high power field) than in the other patients This was also true when the dextrose content of the cerebrospinal fluid was greatly reduced (below 10 mg per 100 cc) as would be expected in view of the fact that the dextrose concentration is lowered because this sugar is utilized as a source of food by the infecting bacteria We have been able to correlate neither the presence of petechiae of bacteremia or of complications nor the height of the leukocyte count in the blood or in the cerebrospinal fluid with the eventual outcome

When the Waterhouse-Friderichsen syndrome is present the prognosis becomes grave It is doubtful whether any patients recovered before the sulfonamide era With the use of these and other modern therapeutic measures about 10 to 25 per cent of these patients survive The outlook would be better still if all the cases were recognized promptly and the patients treated vigorously

Prevention

Contacts should be treated with 1 gm (15 grains) of sulfadiazine twice a day for two days In the event of an epidemic this same dose should be administered to all the members of the group As shown by Kuhns[10] the effectiveness of this procedure depends upon (1) treating all the individuals in the group simultaneously (2) treating all personnel who joined the group subsequent to the institution of prophylaxis and (3) keeping the treated group closed to reinfection from outside sources

Treatment

Sulfonamides The universal success which has resulted from the use of the sulfonamides has made these drugs the mainstay of the treatment of meningococcic infections This is particularly true of *sulfadiazine and sulfamerazine When given systemically by the oral* subcutaneous or intravenous route they diffuse readily into the cerebrospinal fluid This fact combined with the observation that few toxic reactions follow the administration of these two drugs makes them the preferred therapeutic agents in meningococcic meningitis If meningococci are typed from the cerebrospinal fluid by the quellung method or gram negative diplococci are seen in a smear of the sediment or in the tissue juice from a purpuric skin lesion treatment with sulfonamides should be started immediately Sulfonamide treatment should likewise be started if the cerebrospinal fluid contains a predominance of polymorphonuclear leukocytes even though no organ

wound by the characteristic trismus and convulsions and by the absence of leukocytes and bacteria in the cerebrospinal fluid

Other diseases characterized by coma include uremia diabetes alcoholism drug poisoning and cerebral hemorrhage and thrombosis The diagnosis of meningitis should be kept in mind and a lumbar puncture done on all patients in whom coma is not explained with certainty upon some other basis Even in these cases it is important to remember that meningitis and some other cause of coma such as alcoholism may coexist It is a good rule to perform a lumbar puncture whenever there is nuchal rigidity even if the coma seems to be explainable on some basis other than meningitis Epilepsy with convulsions followed by stupor may be mistaken for meningitis The history should serve to make the diagnosis but if it is not available or is uncertain lumbar puncture will settle the matter

Prognosis

Of all the factors which influence prognosis age is the most important Table 39 shows the fatality rates in sulfonamide-treated patients collected from the literature plus our own arranged according to the age of the patients The fatality rate is high for children under one year of age falls and remains low from the age of one to twenty nine years After thirty years it rises slightly increases more sharply after forty and is highest from sixty upward The fatality rate for the entire 1232 cases was 9 9 per cent

TABLE 39

FATALITY RATE IN PATIENTS WITH MENINGOCOCCIC MENINGITIS TREATED WITH SULFONAMIDES ARRANGED ACCORDING TO AGE (FROM VARIOUS SOURCES)

Age (Years)	*Patients Treated*	*Died*	*Per Cent Died*
Less than 1	69	12	17 4
1–4	213	13	6 1
5–9	122	6	4 9
10–19	250	9	3 6
20–29	224	12	5 4
30–39	165	15	9 1
40–49	76	17	22 4
50–59	72	19	26 4
60 and over	41	19	46 3
Total	1232	122	9 9

Another important aid in predicting the outcome is the presence of coma or delirium Among 282 patients treated by us[17] 134 were admitted to the hospital in coma or delirium and of these twenty five (18 7 per cent) died In marked contrast to this only one patient died among the 148 patients who were rational on admission a case fatality rate of 0 7 per cent This patient exhibited the Waterhouse-Friderichsen syndrome and died four hours after admission to the hospital

hour dose should be given initially followed by one sixth of the twenty four hour dose every four hours

DURATION OF SULFONAMIDE THERAPY A lumbar puncture should be performed approximately twenty four hours after sulfonamide treatment is started If the number of organisms has decreased and the sugar content has increased (provided it was below normal originally) the patient can be expected to do well The number of leukocytes in this fluid on the other hand is not significant since either an increase or a decrease is consistent with improvement Further lumbar punctures should be done on any patient in whom coma stupor or delirium or physical signs of meningeal irritation do not disappear within another two or three days or if there is any other reason to suspect that the patient is not doing well If convalescence is uneventful another lumbar puncture need not be performed until after the sulfonamide therapy is discontinued

The temperature usually begins to fall within a short time after the institution of sulfonamide therapy In forty nine of 100 of our patients who recovered the temperature dropped below 101° F and remained there within twenty four hours after treatment was begun In only twelve patients did the temperature remain above this figure for more than ninety six hours after the initiation of treatment Prolonged elevation of temperature or recurrence of fever was observed almost entirely in patients suffering from complications or from toxic reactions caused by the sulfonamides

The clinical picture changes sometimes dramatically sometimes slowly over the course of two to four days The pulse rate drops along with the temperature The vomiting headache and nuchal rigidity disappear usually in that order Sometimes the irrational patient is completely oriented within eight to twelve hours The rapidity of the return to consciousness usually has an inverse relationship to the depth of coma at the start of treatment The leukocyte count of most patients returns to normal limits within one to four days

The rate of return of normal function in damaged nerves varies tremendously Paresis of certain nerves may disappear within the first twenty four hours of treatment On the other hand we have observed a woman with an abducens nerve paralysis who did not regain completely normal balance of her eye muscles until eighteen months after the meningitis and occasionally complete recovery takes even longer Some unfortunates do not regain the function of certain nerves at all This occurs most frequently in the case of the auditory nerve

Arthritis appears soon after the onset in some patients or may develop at any time in the first week or two It may disappear within the first week of treatment or may last for several weeks Permanent disability occurs only rarely

Sulfonamides should be continued until the temperature has been

isms can be seen since the sulfonamides are necessary in the treatment of meningitis caused by other pyogenic organisms and can be supplemented with other agents if the smears or cultures reveal the presence of other bacteria

When the patient is comatose or delirious or shows evidence of peripheral vascular failure an initial dose of 6 gm of sodium sulfadiazine or sodium sulfamerazine should be given intravenously in 500 to 1000 cc of isotonic sodium chloride solution or preferably in one-sixth molar sodium lactate solution (see p 46) If the patient is dehydrated this condition should be corrected by the intravenous administration of fluids before the first intravenous dose of sulfonamide Further doses should be given by slow subcutaneous infusion or through an indwelling stomach tube The latter method is preferable since the regular dose of 1 gm every four hours usually produces adequate concentrations in the blood and the cerebrospinal fluid

The employment of the subcutaneous route of administration necessitates frequent determinations of the concentration of the drug in the blood since the amounts appearing in the blood and spinal fluid cannot be predicted in any given case Usually it is found that 1 gm of sodium sulfadiazine or sodium sulfamerazine every six to eight hours will yield adequate blood and spinal fluid levels The concentrations of the sulfonamides in the cerebrospinal fluid will vary from one half to three-fourths of those observed in the blood In our opinion it is not necessary as a routine measure to determine the amount present in the cerebrospinal fluid since sufficiently high concentrations there are usually assured in the presence of adequate concentrations in the blood

The above dosage schedules are for adults Infants and children should receive from 0 06 to 0 1 gm (1 to 1½ grains) per pound of body weight for each twenty four hour period One half of the estimated twenty four hour dose should be given as an initial dose intravenously in the form of the sodium salt dissolved in at least 500 cc of fluid no matter how small the child One sixth of the twenty four hour dose of sulfadiazine or sulfamerazine should be given every four hours thereafter if it can be administered by stomach tube If subcutaneous infusions must be relied upon one third of the twenty four hour dose may be given at eight hour intervals but the doses must be controlled by determinations of the concentration of the drug in the blood

When the patient is not comatose delirious or in a state of vascular failure it is best to administer the drug by mouth since the proportion of patients with renal complications is definitely higher when the intravenous and subcutaneous routes are used The doses are 6 gm at the start and 1 gm every four hours for adults and for children from 0 06 to 0 1 gm (1 to 1½ grains) per pound of body weight for each twenty four hour period One half the calculated twenty four

200 000 to 300 000 units a day and intrathecally in doses of 20 000 units every twenty four hours *We have resorted to penicillin at such* a time in two patients one of whom died in spite of it but the other who was in peripheral vascular collapse improved dramatically after the penicillin was started

Specific Serum Before sulfonamides were available the only effective treatment in meningococcic meningitis was specific antimeningococcic serum Case fatality rates in patients treated with serum varied from 20 to over 60 per cent depending upon the severity of the cases and the age groups represented When sulfonamide therapy resulted in fatality rates considerably lower than these the use of serum was limited to patients who did not respond to these drugs within twenty four to forty-eight hours Since penicillin is so much safer and has been found at least as effective for this purpose serum is now being discarded altogether

General Measures *Headache may be relieved with aspirin or codeine* or will often require *morphine* Although some observers feel that morphine may be used only in small doses we have seen no ill effects from using amounts sufficient to control headache restlessness or delirium Lumbar punctures have been advised for relief of the headache but we have not found them beneficial They may be helpful however in controlling restlessness or delirium due to increased intracranial pressure as indicated by a falling pulse rate and a rising pulse pressure When a lumbar puncture is done for this purpose the operator should use a needle of small caliber and allow the fluid to escape slowly Delirium from other causes should be treated with barbiturates chloral hydrate paraldehyde or morphine These patients are seldom maniacal and can usually be handled with a minimum of sedation if adequate nursing care is available

FLUIDS Patients treated with sulfonamides should always receive sufficient fluids to insure an output of at least 1500 cc of urine a day In most infectious diseases this requires that 3000 to 4000 cc of fluids be administered during each twenty four hour period Patients with meningitis often need more than this because they are dehydrated from vomiting This is especially true at the start of treatment when a large intravenous dose of a sulfonamide given to a dehydrated patient may produce obstruction in the renal tubules within the first few hours of treatment If there has been vomiting or if there are any other evidences of dehydration when treatment is started 1000 to 3000 cc of fluid should be given intravenously and subcutaneously in addition to the solution in which the sulfonamide is dissolved

DIET During the acute stage the patient will eat little As he improves a soft high caloric diet should be given

NURSING CARE The patient should be kept warm and turned frequently if he is comatose or stuporous Precautions should be taken

within normal or nearly normal limits for about a week A day or two after this therapy is stopped another lumbar puncture may be done. If the white blood cells are thirty or less per cu mm if the cerebrospinal fluid is normal in all other respects and all other evidences of active infection are gone we have made it a practice to discharge the patient None of our patients discharged on this basis has returned with a recurrence of the meningitis If the leukocyte count is above 30 per cu mm the lumbar punctures should be repeated at weekly intervals until the leukocytes reach that figure

Penicillin Since the meningococcus is sensitive to penicillin this would be a desirable agent for the routine treatment of meningococcic meningitis were it not for the fact that it penetrates poorly into the cerebrospinal fluid (see p 76) In order to insure the presence of adequate concentrations the drug must be given by lumbar puncture every day or at least every other day Meads[12] treated nine patients with meningococcic meningitis with intrathecal doses of 10 000 to 20 000 units of penicillin initially followed by 5000 to 15 000 units at twelve hour and later at twenty four hour intervals The patients received in addition 10 000 or 15 000 units intramuscularly every three hours In all the patients except one who had received sulfadiazine before admission to the hospital clinical improvement was slow and in seven the meningococci could still be cultured from the cerebrospinal fluid or seen on smear twenty four hours to seven days after treatment was begun Three patients had to be given sulfonamides in order to make recovery certain This investigation has been cited in some detail because it confirms the opinion we have formed from our own experience that adequate sulfonamide therapy is superior to penicillin in the treatment of meningococcic meningitis

Whether penicillin should be added to sulfonamides routinely in the treatment of this disease is doubtful except in patients with an overwhelming infection and evidences of peripheral vascular collapse in other words the Waterhouse Friderichsen syndrome Penicillin sterilizes the blood stream promptly probably more rapidly than the sulfonamides do Accordingly when this syndrome is present it is best to give sulfadiazine or sulfamerazine intravenously from the start and penicillin in doses of 200 000 to 500 000 units a day either by continuous intramuscular infusion intravenous infusion or intramuscular injections repeated every two hours

Occasionally a patient may be encountered who is hypersensitive to sulfonamides in general Such a patient may be treated with penicillin alone

In other patients it is our opinion that penicillin may be withheld until it is evident that they are failing to improve or growing worse after twenty four to forty-eight hours of sulfonamide therapy Then penicillin may be administered systemically in amounts totalling

to prevent decubitus ulcers especially if he is incontinent The eyes should be kept clean and watched for evidence of infection The joints should be inspected and palpated for evidences of arthritis Purpuric rashes should be watched since they sometimes become gangrenous

Treatment of the Waterhouse-Friderichsen Syndrome Prompt recognition and treatment are imperative if the patient s life is to be saved The initial dose of sulfadiazine or sulfamerazine should be given intravenously and subsequent doses either subcutaneously or orally One half million units of penicillin should be administered during each twenty four hour period either by continuous intravenous or intramuscular infusion or by intramuscular injections at two hour intervals Since peripheral circulatory collapse is an outstanding feature several measures are employed to combat it These include the administration of large amounts of isotonic sodium chloride solution intravenously epinephrine and adrenal cortical extract or desoxycorticosterone Large doses of ascorbic acid have also been advocated since the adrenal glands which ordinarily store vitamin C are usually damaged in that syndrome It is difficult to assess the value of these measures inasmuch as recoveries have occurred only when antibacterial agents have also been used Until more evidence can be gathered treatment with a combination of these therapeutic measures seems to be the wisest course

Treatment of Complications The treatment of the disease is the only treatment for injury to the nerves Paralysis may improve during the acute illness during the weeks immediately following or over the course of months or even years afterward Narrowing of the visual fields and deafness from involvement of the second and eighth nerves respectively may improve after the acute disease is over but are more likely to be permanent than affections of the other nerves

Arthritis and tenosynovitis usually improve under sulfonamide treatment If not a course of penicillin in doses of 25 000 units every three hours should be given for as long as three or four weeks if necessary If the joint fluid should become purulent it should be aspirated and 50 000 units of penicillin injected into the joint cavity on alternate days until signs of inflammation have disappeared The instillation of penicillin into the joint cavity may likewise be given a trial in any case where cure is not forthcoming when penicillin is administered intramuscularly

Treatment of Contacts Meningococci are so highly sensitive to sulfonamides that they will disappear from the pharynx of contacts in nearly *every instance after the administration of small doses of* these drugs Accordingly it is the best policy to treat all contacts in the family or institution where the patient lived by giving them 1 gm of sulfadiazine twice a day for two days It is important that all

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Treatment of Complications The treatment of the disease is the only treatment for injury to the nerves Paralysis may improve during the acute illness during the weeks immediately following or over the course of months or even years afterward Narrowing of the visual fields and deafness from involvement of the second and eighth nerves respectively may improve after the acute disease is over but are more likely to be permanent than affections of the other nerves

Arthritis and tenosynovitis usually improve under sulfonamide treatment If not a course of penicillin in doses of 25 000 units every three hours should be given for as long as three or four weeks if necessary If the joint fluid should become purulent it should be aspirated and 50 000 units of penicillin injected into the joint cavity on alternate days until signs of inflammation have disappeared The instillation of penicillin into the joint cavity may likewise be given a trial in any case where cure is not forthcoming when penicillin is administered intramuscularly

Treatment of Contacts Meningococci are so highly sensitive to sulfonamides that they will disappear from the pharynx of contacts in nearly every instance after the administration of small doses of these drugs Accordingly it is the best policy to treat all contacts in the family or institution where the patient lived by giving them 1 gm of sulfadiazine twice a day for two days It is important that all

COMPLICATIONS

Meningitis is the most frequent complication In any large series of patients with meningitis many give a history characteristic of acute meningococcemia before they were seen by the physician Among Campbell s patients with the chronic form twenty five developed meningitis

Other complications are endocarditis pneumonia nephritis pericarditis multiple abscesses thrombophlebitis and conjunctivitis Sloughing of purpuric lesions is sometimes seen

DIAGNOSIS

Meningococcemia should be suspected when a patient exhibits a maculopapular petechial or purpuric rash low or moderately high fever and pain in one or more joints It must be considered as a possibility even if joint symptoms are absent During an epidemic a presumptive diagnosis can be made on the basis of physical findings alone but at other times this is unlikely Final diagnosis depends in every instance upon culture of the organisms from the blood stream or from the tissue juice from a punctured purpuric area We believe that a lumbar puncture should always be done since this is the only way to make sure whether meningitis is present In our opinion there is no reason to fear that performing a lumbar puncture in the presence of bacteremia will precipitate meningitis

In the differential diagnosis of meningococcemia we must consider other diseases which cause fever and joint pains such as gonococcic endocarditis rheumatic fever acute rheumatoid arthritis the secondary stage of syphilis and bacterial endocarditis caused by the *Streptococcus viridans* A history of recent venereal infection should make one suspect gonococcic or luetic infection In rheumatic fever and rheumatoid arthritis a rash is not often present In acute rheumatoid arthritis the involvement of the joint is great in proportion to the amount of fever and constitutional reaction whereas in meningococcemia the opposite is true In *Streptococcus viridans* endocarditis a changing murmur is usually heard and pains when they do occur are usually mild transitory and not accompanied by swelling Symptoms of emboli to the spleen kidneys brain or extremities splinter hemorrhages and Osler s nodes are also often present In spite of these clinical hints however a definite diagnosis cannot be made except bacteriologically

PROGNOSIS

The prognosis is better in meningococcemia than in most bacteremias Some patients recover without treatment while the diagnosis is being made and probably a great many more never even come to the doctor s attention On the other hand most of the patients eventu

ally go on to develop meningitis and share in the prognosis for that disease In patients with chronic meningococcemia Campbell[2] recorded a fatality rate of 33 per cent in patients who received no specific treatment 13 per cent in those who were given serum and 7 per cent in those who received sulfonamides with or without serum in addition

TREATMENT

Sulfadiazine or sulfamerazine should be employed in the same doses and by the same routes as in meningococcic meningitis orally in the patients who are mildly ill and intravenously and subcutaneously in those who are very toxic or show evidences of peripheral vascular collapse Patients in this latter group should also receive auxiliary treatment with penicillin epinephrine adrenal cortical extract and sodium chloride solution as outlined under the treatment of the Waterhouse-Friderichsen syndrome (see p 222) We have never needed to use penicillin in other patients with meningococcemia although it should be helpful as an adjunct to sulfonamides in very toxic patients Penicillin should not be given without the concomitant administration of sulfonamides The reason for this is the poor absorption of the antibiotic into the cerebrospinal fluid Patients with meningococcemia have been known to develop meningitis while under treatment with penicillin alone

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12 Gonococcic Infections

The gonococcus (*Diplococcus gonorrhoeae*) is a gram-negative coffee-bean shaped coccus occurring in pairs and found both intracellularly and extracellularly in purulent exudates. While it infects particularly the mucous membranes of the genitourinary tract, it often involves mucous membranes elsewhere, such as the conjunctiva and rectum, and also has a predilection for serous surfaces, such as the endocardium, the meninges and the membranes lining joints and tendon sheaths. Because of the diversity of clinical syndromes caused by the gonococcus, certain general procedures of diagnosis will be discussed first, after which the individual gonococcic infections will be considered.

Laboratory Diagnosis of Gonococcic Infections

STAINED SMEARS

Exudates from lesions of the mucous membranes, or the centrifuged sediment of fluids from synovial or other cavities, may be spread on a slide and stained by Gram's method. Identification of the organisms as gram-negative diplococci by means of stained smear is rapid and simple. If dependence is placed upon this method alone, however, gonococci will not be detected in some cases in which they are actually present, or other gram-negative cocci may be erroneously called gonococci. These possibilities of error are considerably diminished by taking cultures of suspected exudates.

CULTURES

Recent work has shown that gonococci are not so difficult to grow as was formerly supposed, provided certain procedures are followed.

(1) Implants of suspected material upon culture media should be made directly from the patient, or as soon as possible after the material is obtained. If plating cannot be done immediately, the infected material may be placed in sterile horse blood, from which a culture should be made within twenty-four hours.

(2) An enriching substance should be used in the medium, such as starch, blood serum or ascitic fluid.

(3) Cultivation should be carried out in an atmosphere reinforced with about 10 per cent carbon dioxide.

(4) A 1 per cent aqueous solution of dimethyl para-phenylene-diamine may be spotted upon suspicious colonies. This will cause colonies of gonococci (and also other *Neisseriae*) to stain pink, later maroon

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urethritis perhaps in all of them When the prostate is inflamed there may be acute retention of urine as a result of compression of the posterior urethra Pain in the suprapubic and inguinal regions or over the sacrum or the hip on the affected side may result from involvement of a seminal vesicle Inflamed seminal vesicles are enlarged and tender

Chronic Gonorrhea In untreated or inadequately treated patients the *infection often goes into a chronic stage which varies greatly in* severity from patient to patient Some become symptomless carriers who because of the absence of discomfort to themselves are especially insidious menaces to the health of others Other victims of the chronic form of the disease continue to have some discharge or perhaps only a morning drop of mucus at the end of the urethra They may have urgency and frequency of urination and pain or burning referred to the glans penis especially on urination Pain may occur in the perineal or inguinal regions in the lower back and down the thighs The prostate and seminal vesicles may be swollen and tender

Complications

Local Complications In anterior urethritis these are balanitis *balanoposthitis paraurethritis paraurethral abscess and cavernitis* Later strictures of the urethra may occur The complications of posterior urethritis other than prostatitis and seminal vesiculitis are epididymitis and prostatic abscess Seminal vesicular abscesses and generalized cystitis are much less frequently encountered complications

Systemic Complications These are discussed under Infections in Other Parts of the Body beginning on page 240

Obtaining Material for Culture

In males urethral secretions should be obtained before the patient voids by wiping the end of the penis with sterile cotton obtaining secretion upon a sterile swab and inoculating it directly at the bedside Stripping the urethra may be necessary to obtain a sufficient amount of material In patients who have no urethral secretion it is best to take a culture from the urethra after stripping and a culture of the *centrifuged sediment of the urine If gonococci cannot be grown from* either of these materials and the disease is still suspected the prostate and *seminal vesicles may be massaged gently* and this secretion cultured

Diagnosis

While the sudden onset of purulent urethral discharge after questionable sexual exposure is presumptive evidence of a gonococcic infection the diagnosis should not be made unless intracellular gram negative diplococci of the characteristic shape are seen on smear and preferably are obtained by culture In cases where the disease has become chronic

and then black. Because it results from the production of oxydase by the gonococcus, this is known as the oxydase test. Fermentation reactions are necessary to differentiate the gonococci with certainty from other gram negative cocci.

By these procedures a high percentage of positive cultures can be obtained, and gonococci can often be grown from material in which they cannot be identified by the stained smear method. Cultures are recommended (1) to establish the diagnosis in questionable cases, (2) to verify cure when gonococci are no longer found on stained smear, and (3) to differentiate gonococci from other organisms of similar morphology when the material is obtained elsewhere than the genitourinary tract or in medicolegal cases.

Complement Fixation Tests

Among the serologic tests that have been used in the diagnosis of gonococcic infections, the complement fixation test is the only one of practical value at the present time. It usually becomes positive within a few weeks after the initial infection and remains positive for the duration of the infection or sometimes for several weeks or longer after the infection is cured. Consequently, this test is of little value in the diagnosis of acute local infections. Since there is considerable dispute as to whether the test often remains positive for a long time after the gonococci have been eradicated from the body, other methods are superior for the determination of cure. Its greatest usefulness is in the differentiation of gonococcic arthritis from other joint diseases. It will be discussed in more detail in the section on Arthritis.

Infections of the Genitourinary Tract in Men

Symptoms and Signs

Acute Anterior Urethritis. Except in rare instances, infection is by sexual contact, the incubation period after exposure being two to five days in the majority of cases, although it may occasionally extend as long as fourteen days. The first abnormal sensation is tingling in the urethra. This is followed by burning, which is more intense upon urination. Purulent secretion appears and becomes profuse in the majority of patients. Redness and swelling of the external meatus and tenderness of the urethra to palpation are the physical signs. In patients who do not receive the sulfonamides or penicillin, the acute stage of the infection lasts from two to six weeks.

Acute Posterior Urethritis. In many patients the infection extends into the posterior urethra, causing frequency and urgency of urination, perineal discomfort and sometimes terminal hematuria.

Acute Prostatitis and Seminal Vesiculitis. The prostate and seminal vesicles are affected in the majority of patients with acute posterior

would still seem advisable to use the injection method which makes absolutely certain that the patient receives the prescribed amount and that treatment is not stopped short of this Instillation of penicillin directly into the urethra has not produced cure in gonorrhea and should not be used

Subjective sensations diminish within a few hours after the initiation of treatment and the discharge decreases and becomes mucoid after a period varying from a few hours to several days In about one fifth of the patients a slight mucoid discharge will continue for one to three weeks This is not indicative of a continued infection and disappears eventually Repeated stripping of the urethra is often responsible for the prolonged discharge Bacteria are no longer found in the stained smears and cultures within from one hour to several days after the beginning of treatment

When the infection has not been completely eradicated the discharge may become scanty and mucoid or cease altogether and smears and cultures may become negative Then after a few days to a week or more the discharge will again increase and become purulent and positive smears and cultures will reappear In order that a latent infection may be discovered and relapses be detected it is advisable to have the patient report forty eight hours and again seven fourteen and twenty-one days after the end of treatment At these times a smear of the urethral discharge should be taken and preferably cultures also At the end of a month or later bulbous bougies and sounds should be passed in order to determine whether strictures are present and also to stir up any latent infection that might be present

If a relapse occurs another course of penicillin should be given While many cases of relapse can be cured when the dose used in the second course is no larger than that administered the first time it is perhaps best to give twice as much the second time This may be done by administering two doses of 300 000 units each in beeswax and oil intramuscularly at twelve hour intervals If intermittent injections are used 30 000 to 50 000 units can be given every two hours for twelve doses The follow up after this course should be as rigid as after the first and if relapse again takes place another course of penicillin should be given using the same or even higher doses as may seem necessary It is of course important to make sure that the infection is actually a relapse and not a new infection since the latter should be amenable to the same doses as the first infection

Franks[4] has reported the development of penicillin resistant gonococci in four patients and other cases will doubtless be encountered as more patients are treated with penicillin When this occurs sulfonamides fever therapy or streptomycin may be used It should be emphasized however that instances of patients being infected with gonococci which were proved to be penicillin resistant have been rare

or where there are legal reasons cultures may be necessary If no organisms are found on smear of the urethral discharge the urine may be centrifuged and the sediment stained

TREATMENT

Penicillin When exposed to the action of penicillin in vitro the gonococci are among the most susceptible of bacteria This same susceptibility has been illustrated in patients by Miller s[12] demonstration of the disintegration and disappearance of the gonococci causing acute urethral infections in males when 50 000 to 100 000 units of penicillin were given intramuscularly In most instances within two or three hours after the first dose of penicillin was administered the urethral exudate had been reduced in quantity and was more watery in consistency By the sixth hour only a drop of watery secretion could be obtained by stripping the urethra and by the next day even this was gone The symptoms of urethritis disappeared at the same time Smears of the urethral exudate two or three hours after the initiation of treatment showed changes in the shape and staining qualities of the cocci and rapid diminution in the numbers so that they disappeared entirely from stained smears within one to four hours in most cases Degenerative changes in the polymorphonuclear leukocytes paralleled those which occurred in the gonococci Cultures became negative within an hour of the disappearance of the gonococci from the smears

This experience has been paralleled by clinical results In gonococcic urethritis recovery rates of 81 to nearly 100 per cent have been obtained when adequate doses were administered When the intermittent intramuscular method is used the best results are obtained when 200 000 units or more are administered in doses of 10 000 to 20 000 units at one to three hour intervals These doses maintain fairly high concentrations of penicillin in the blood for ten to twenty hours In general the higher the dosage and the greater the number of individual injections the higher the percentage of cures[11] Similarly good results without the necessity of frequent injections can be obtained by giving one injection of a penicillin oil beeswax mixture Because of its simplicity the latter method is recommended as the most suitable treatment We suggest that after the diagnosis is established an intramuscular injection of 300 000 units of penicillin in oil and beeswax (which is the amount contained in 1 cc of most preparations) be given If the beeswax-oil preparation is not advisable for any reason 10 000 units in aqueous solution may be given intramuscularly followed by 10 000 units one hour later 10 000 units at the end of two hours and 80 000 units at the end of three hours

In view of the large amounts of penicillin necessary and the uncertainties of absorption when the oral route is employed this method is not recommended Even if these disadvantages were overcome it

Sulfonamides may still be used in the occasional cases in which the gonococci have become so highly resistant to penicillin that large doses of the antibiotic have failed to eradicate the infection

If sulfonamides are used the drug of choice is sulfathiazole which should be given in full doses of 4 gm (60 grains) initially followed by 1 gm (15 grains) every four hours Sodium bicarbonate should be given concomitantly 6 gm (90 grains) with the first dose and 3 gm (45 grains) with each succeeding dose and at least 3000 cc of fluids should be given each day Sulfadiazine may be substituted for sulfathiazole when the patient is sensitive to the latter drug Treatment *should be continued for at least five days* If the infection is not well under control or cured within ten days and there are no complications present to explain the lack of response the sulfonamide treatment may be considered a failure and discontinued

Combined penicillin and sulfonamide therapy has shown promising results[2, 14] Further studies must be carried out with various combinations of antibiotic and sulfonamide before it can be determined whether the two agents together are superior to penicillin alone

Streptomycin Gonococci have been shown to be susceptible to streptomycin in vitro and Putnam[17] and Pulaski[14] have demonstrated that many patients with gonorrhea are cured by this antibiotic The former investigator administered 0 1 gm intramuscularly every hour for five doses while Pulaski gave six doses of 0 5 gm every three hours Since the development of penicillin resistance in a given strain of gonococcus does not influence its susceptibility to streptomycin the latter antibiotic may be used in cases where a cure is not obtained because of penicillin resistance but further investigation is necessary to determine the optimal dosage and the possibility of the development of streptomycin resistant gonococci

Fever Therapy The ease with which gonococci are killed by heat has led to the use of artificial fever to cure gonococcic infections which do not respond to the sulfonamides Fever may be induced either by placing the patient in a fever cabinet or by the injection of foreign protein such as typhoid vaccine The height of the fever is less predictable and the levels are generally lower when the latter method is used The employment of a fever cabinet requires a trained attendant but has the advantage that the patient s temperature can be raised to a desired point and kept there for a predetermined period or brought down promptly if the occasion demands

The susceptibility of different strains of gonococci to high temperatures is independent of their susceptibility to sulfonamides (and probably also independent of their susceptibility to penicillin) Furthermore both penicillin and the sulfonamides will be more efficacious at these higher temperatures As a consequence fever therapy can be used as a last resort in patients who do not respond to simpler methods

up to the present time In most of the cases where penicillin therapy is reported to have failed a structural defect was probably the cause for instance a walled off abscess or poor drainage due to a stricture or a congenital malformation and so forth These conditions require the establishment of adequate drainage which should be accompanied by several days of penicillin therapy rather than a shift to another drug

PENICILLIN TREATMENT WHEN SYPHILIS IS PRESENT AT THE SAME TIME As the employment of penicillin in the treatment of gonococcic infections becomes more widespread the problem of coexistent syphilis assumes major importance The incubation period of syphilis is longer than that of gonorrhea and a considerably larger amount of penicillin is required to treat syphilis adequately A patient acquiring both diseases at the same time would in many instances be under treatment for the gonorrhea before any evidence of syphilitic infection appeared Consequently the evidences of syphilitic infection might be delayed or even fail to appear altogether with the result that the patient would enter the latent stage of syphilis without detection If a developing chancre passes unnoticed when penicillin therapy is started it may become dark field negative and will probably disappear If it returns at all it will not be likely to do so until some weeks after the penicillin was administered This subject has been ably reviewed by Walker[34] whose suggestions are incorporated in the following recommendations

1 Every patient with gonorrhea should be examined carefully for evidences of syphilis and blood should be taken for a serological test before penicillin treatment is started In the event that suspicious lesions are found penicillin therapy may be delayed until a definite diagnosis can be made or sulfonamides may be given instead

2 All patients treated for gonorrhea with penicillin should be examined at monthly intervals for at least three months after the completion of treatment and a serological test for syphilis should be taken at the end of that period Any patient who shows an unusual reaction to penicillin which might possibly be interpreted as a Herxheimer reaction (see p 86) should have frequent physical examinations and serological tests for syphilis for several months after the penicillin therapy

Sulfonamides Before penicillin came into use the sulfonamides were universally employed in the treatment of gonococcic infections The percentage of cures varied from 30 to 90 per cent depending upon the drug and dosage employed and upon the degree to which the individual strain of gonococcus had become resistant to sulfonamides At present the sulfonamides have been almost completely superseded by penicillin principally because of the development of strains resistant to sulfonamides and the short period of treatment required when penicillin is employed

gonococci do not persist longer than three months and that the symptoms which appear after this time are due to secondary invaders or to reinfection.

Complications

Local Complications. The gonococcic infection characteristically spreads *from the primarily infected areas into related structures.* The most common of these are: from the urethra into Skene's ducts; from the labia into Bartholin's glands; from the cervix into the fallopian tubes and ovaries, forming abscesses in the tubes, in the ovaries or at the junction of the ends of the tubes and the ovaries; and also pelvic abscesses.

Symptoms of salpingitis include pain in the lower abdomen and back, menorrhagia and metrorrhagia, frequent and uncomfortable urination and vaginal discharge. Fever, increased pulse rate, leukocytosis and a rapid sedimentation rate are often found. On examination there is tenderness in one or both lower quadrants of the abdomen. *Bimanual* palpation elicits pronounced tenderness of the pelvic organs. Masses are *not usually present at first.* Later they are felt in one or both adnexae.

Gonococcic peritonitis in the upper part of the abdomen, although not common, is a characteristic and striking complication. There is sudden onset of sharp pain in the upper part of the abdomen, most *often on the right side, often referred to the area behind the clavicle.* Chill and fever may be present, nausea frequently, vomiting seldom. Examination reveals tenderness and spasm in the right upper quadrant of the abdomen and sometimes a friction rub can be heard along the anterior costal margin. After a few days of acute symptoms the pain *lessens and gradually disappears. Complete recovery within four weeks* is the rule. The subsidence of the acute process leaves behind characteristic violin string adhesions between the liver and the diaphragm. Stanley[9] has reported that 20 000 units of penicillin administered every three hours for sixteen doses is sufficient to cure the condition.

Gonorrhea after the Menopause. When a gonococcic infection occurs after the menopause, it often takes the form of a vulvovaginitis. Complications may occur, however, in the upper genital tract, such as salpingitis, tubovarian abscess and so forth.

Systemic Complications. These are discussed under "Infections in Other Parts of the Body," beginning on page 240.

Obtaining Material for Cultures

Culture of the vaginal secretion often fails to yield gonococci, especially if the infection is not in the acute stage. Consequently it is important to obtain secretions from pockets where the infection "holes

Kendell[8] has shown how the course of treatment has changed over a period of years from five hour sessions at 105° to 106° F twice a week to one or two ten hour sessions at 106° to 107° F The reader is referred to his article and that of Desjardins[3] for details

General Treatment In spite of the fact that most patients with local gonorrheal infections are allowed to remain ambulatory the disease should not be considered as affecting one part of the body to the exclusion of the rest The infection may spread to organs outside the genitourinary tract with serious and sometimes fatal consequences Furthermore the patient s general physical condition will affect the outcome of the genitourinary infection The patient should obtain sufficient sleep and whatever rest he can during the day Moderate or violent exercise sexual excitement and the use of alcohol should be avoided entirely until recovery is complete

Local Treatment Various antiseptic solutions used for local irrigation in the past are being discarded It is doubtful whether the effect on the organisms was ever of sufficient magnitude to be of curative value Their usefulness was more likely due to a stimulative action upon the tissues of the host

Treatment of Local Complications When local complications are present in the genitourinary tract penicillin treatment will usually be needed for several days in doses of 300 000 to 600 000 units in oil and beeswax or 30 000 to 50 000 units every three hours in aqueous solution intramuscularly Surgical measures may also be required in some cases

Infections of the Genitourinary Tract in Women

Symptoms and Signs

Acute Urethritis and Cervicitis The urethra is affected in about half of the women with gonococcic infection The infection usually involves the entire length of the urethra and the trigone of the bladder giving rise to symptoms of frequency urgency and burning or pain on urination These may be so slight as to pass unnoticed although they are usually more pronounced and are sometimes incapacitating Purulent urethral discharge is present and occasionally hematuria Sometimes the cervix alone is affected but more commonly the cervix and urethra together The cervix is inflamed and edematous and covered with yellow pus

Chronic Gonorrhea Both the urethritis and the cervicitis may and if untreated or inadequately treated often do go into a symptomless stage in which the organisms lie buried in glands and crypts and are difficult to find even on cultures Some observers claim that acute flare-ups may occur at any time as a result of sexual excess overuse of alcohol or poor general physical condition Others believe that

mucus either by cotton wrapped applicators or a suction apparatus. After the canal has been thoroughly cleansed compress the cervix in the manner shown to force out the glandular secretion and secure it upon the cotton wrapped applicators (Fig 36)

Diagnosis

The diagnosis of gonorrhea in women is usually much more difficult than in men since it may be entirely asymptomatic or may become chronic and exhibit no evidences of infection. Every attempt should



Fig 35 Method of obtaining secretions from Bartholin's glands. (*V D Bulletin* No 97 U.S. Public Health Service)

be made to verify or exclude the diagnosis of gonorrhea when infection of the urethra and adjacent glands of the cervix or of the fallopian tubes is present. Repeated stained smears and cultures are necessary before such an infection can be declared definitely nongonorrheal.

Treatment

Treatment with penicillin sulfonamides and fever therapy is the same as in gonorrhea in the male when the patients are treated during the first day or two of the disease. The reader is referred to the discussions on page 230 to 234 for this information. Since effective anti

up The technique for doing this has been excellently described by Pelouze[15] as follows

Skene's Glands Cleanse the urethral meatus with dry cotton Digitally strip the entire urethra paying particular attention to the lower half inch Pass a small cotton wrapped applicator one half inch into the meatus and rub it into the floor of the urethra whether macroscopic fluid is expressed or not (Fig 34)

Bartholin's Glands Cleanse the opening of the duct at the junction of the middle and posterior third of the lesser labia with dry

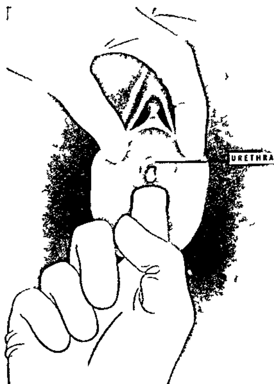


Fig 34 Method of obtaining secretions from Skene's glands (V D Bulletin No 97 U S Public Health Service)

cotton With a finger in the vagina and the thumb externally compress the intervening structures at a point halfway from the duct opening to the midline posteriorly and collect even the slightest moisture for study (Commonly the quantity obtained is so slight it would be lost on a cotton wrapped applicator A platinum loop or the flat end of a toothpick may serve better) (Fig 35)

Endocervical Glands Introduce a bivalve vaginal speculum so that the uterine cervix rests between the ends of its blades (If cultures are to be employed the speculum should be introduced wet—no lubricant should be employed) Thoroughly remove the cervical plug of

Treatment of Pelvic Inflammatory Disease For late cases and *particularly in patients with pelvic inflammatory disease doses of* 250 000 to one million units or more of penicillin a day must be given for a period of at least three days and usually longer While patients with mild cases of pelvic inflammatory disease usually respond well penicillin does not always produce the desired result in severe cases and in those in which the process is chronic These patients may relapse unless penicillin treatment is continued for long periods of time and chronic foci of infection may become established in spite of apparently adequate doses Nevertheless penicillin is beneficial in that it diminishes the general toxicity reduces the chances of spread and decreases the hazard of surgical intervention should it be required

Other measures which should be used are (1) Rest in bed (2) Avoidance of alcohol and sexual stimuli (3) Hot or cold applications to the abdomen whichever give relief (4) For the relief of pain acetylsalicylic acid in doses of 0 6 to 1 0 gm (10 to 15 grains) combined if necessary with codeine in doses of 0 03 gm (½ grain)

An operation is seldom if ever necessary during the period of the acute inflammation

Vulvovaginitis in Children

While the vagina in adults is resistant to infection with the gonococcus it is readily infected in girls before puberty along with the vulva The infection is spread by contact with contaminated articles or with infected children or adults

Symptoms and Signs

Itching and burning of the vulva and vagina are accompanied by a thick or watery purulent discharge Urination may be frequent and painful The labia are swollen red and matted together The urethral orifice is red and a discharge may be seen pouring from it The hymen is red and may be eroded The cervix is red and swollen. The acute stage may subside after two to four weeks but often takes months to disappear altogether

Diagnosis

Inflammation of the vulva and vagina in a child should always make one suspect a gonococcic origin The history of a suspicious contact makes this more certain The diagnosis can only be made with certainty however when the organisms are obtained by culture of the discharge

Complications

Proctitis is the most frequent of the complications affecting adjacent structures Ascent of the infection into the tubes or into the bladder

bacterial agents have been in use local treatment has not been needed Douches are probably best dispensed with since forceful ones may

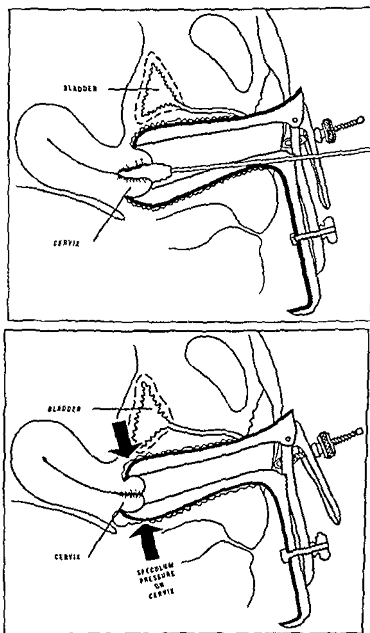


Fig 36 Method of obtaining secretions from the endocervical glands (V D Bulletin No 97 U S Public Health Service)

spread the infection and the physician cannot prescribe the force with which they are to be used

and the meninges The conjunctivae are most often infected by direct contact or by infected hands

Gonococcic Arthritis and Tenosynovitis

At least 2 per cent of patients with gonorrhea developed arthritis as a complication in presulfonamide days The incidence is probably less than this in patients properly treated with penicillin or sulfonamides Although the onset of the arthritis may be coincident with that of the genitourinary infection this complication more often appears one to two weeks after the first local symptoms In other patients the joint disease may begin when the genitourinary disease is diminishing or may develop months or even years after all evidences of local infection have disappeared

The age distribution of gonococcic arthritis corresponds closely with the period of greatest sexual activity although occasional cases occur in young girls with vulvovaginitis and in patients in the sixth and seventh decades Among 200 cases studied by us 70 per cent of the patients were between the ages of twenty and thirty nine years Fifty four per cent were males and 46 per cent females

Symptoms and Signs

At first the patient complains of pain in one joint usually one of the larger ones Within a day or two other joints begin to be affected As the process spreads to the other joints those originally involved

TABLE 40

Joints Involved in [illegible]00 Cases of Gonococcic Arthritis

Joint	*Number of Cases*
Knees	1[illegible]9
Ankles	13[illegible]
Wrists	8
Hips	66
Shoulders	[illegible]
Elbows	[illegible]1
Metatarsal and phalangeal	3
Metacarpal and phalangeal	18
Lumbar and thoracic spine	1[illegible]
Cervical spine	
Sternoclavicular	
Temporomandibular	2
Number of Joints Involved	
One	41 cases
Two	41 cases
Three	44 cases
Four	33 cases
Five or more	41 cases
Total	[illegible]00 cases

may revert immediately to the normal state More often they remain painful for some time The migratory type of arthritis is more characteristic of gonococcic infection than the monarticular type as was

is rare The complications elsewhere in the body are similar to those found in adults

TREATMENT

Penicillin Since this antibiotic is more effective than the sulfonamides in other genitourinary infections caused by the gonococcus it should be the agent of choice in vulvovaginitis At the present time an insufficient number of patients have been treated to permit an exact determination of the optimal dose Sweet[22] found that a total dose of 50 000 units for children under six years of age and 100 000 units for older children administered in divided doses over a period of twelve hours was successful in eradicating the infection

Sako[18] obtained fifteen cures among sixteen patients treated with a single intramuscular dose of 100 000 units The patient who failed to respond recovered after receiving 10 000 units every three hours for eight doses

Sulfonamides Sulfathiazole sulfadiazine or sulfamerazine may be given if desired in doses of 0 03 to 0 06 gm (½ to 1 grain) per pound of body weight for each twenty four hour period divided into four or six doses Treatment should be continued for ten days to two weeks In most patients the discharge is observed to be lessened by the second or third day of treatment Smears and cultures usually become negative by the seventh to fourteenth day Ten to 20 per cent of patients will have a recurrence a great many of which probably represent new infections These should be given penicillin

Estrogenic hormone given orally hypodermically or in the form of vaginal suppositories was used in presulfonamide days in order to change the vaginal membrane to the adult state and thus render it more resistant to gonococci This method has now been generally discarded as less effective than sulfonamides or penicillin

Other Measures In view of the effectiveness of present day therapy local treatment can be limited to Sitz baths or gentle lavage Strict precautions should be taken to prevent spread with particular attention to the disposal of clothing and towels and the cleansing of toilet seats after use by the patients A search should be made for the person who was the source of the infection lest the patient become reinfected after cure

Infections in Other Parts of the Body

Moderate and severe cases of gonococcic genitourinary infection are attended by general symptoms and bacteremia undoubtedly occurs much more often than it has been detected The gonococcus is transported by the blood to distant sites and seems to choose especially other mucous membranes such as the conjunctivae or serous membranes such as the lining of joints and tendon sheaths the endocardium

Blood The leukocytes are usually increased sometimes reaching 30 000 per cu mm Blood cultures are positive in a small percentage of cases The sedimentation rate is elevated during the acute stage of the disease and returns to normal as the active infection leaves Hypochromic anemia often develops when the illness is prolonged

The complement fixation test finds its greatest usefulness in the diagnosis of this complication of gonorrhea Warren[24] stated that this test was positive in 86 5 per cent of 125 serums from seventy four patients with proved or probable gonococcic arthritis He found only occasional *false positive tests in patients with other types of arthritis* We found positive complement fixation tests in 82 per cent of seventy eight patients with gonococcic arthritis

X ray Examination In the early stages and throughout the entire course when the arthritis is mild the only roentgenological changes are in the soft tissues In the more severe cases destruction of the cartilage may take place even as early as two or three weeks after the onset Some decalcification of the adjacent bones may also be present

Diagnosis

Arthritis which involves several joints which is accompanied by fever and leukocytosis and is preceded or accompanied by a local *genitourinary infection is most likely caused by gonococci* If these organisms are cultured from the blood or synovial fluid the diagnosis may be considered certain If they are obtained from the genitourinary tract or if the complement fixation test is positive this may be considered presumptive evidence that the gonococci are causing the arthritis

Differential Diagnosis The clinical syndrome just outlined may be present in rheumatoid arthritis and in acute rheumatic fever Rheumatic polyarthritis is especially likely if there is a history of repeated sore throats or of chorea if cardiac abnormalities are present (especially a *lengthened PR interval in the electrocardiogram) or if the* arthritis improves dramatically within two or three days when large doses of salicylates are administered Confusion may occur however because the pain in gonococcic arthritis is often diminished considerably by salicylates while swelling and other local signs may subside as a result of the concomitant bed rest Rheumatoid arthritis has few distinguishing features and often can be ruled out only by finding evidence to substantiate the diagnosis of gonococcic infection

Although high blood leukocyte counts may be found in all kinds of arthritis the highest counts and the greatest increase in the percentage of polymorphonuclear cells are present *in arthritides caused* by bacteria gonococci meningococci staphylococci streptococci or pneumococci These organisms almost always cause arthritis as a

formerly taught Among our patients 159 (80 per cent) gave a history of involvement of more than one joint (Table 10)

Although the joint pain is usually dull and aching in character it may vary from a slight ache all the way to a pain so severe as to cause the patient to cry aloud if he does not get relief

On examination one or more joints will show varying degrees of swelling redness and heat The swelling may be caused by fluid within the capsule or by periarticular inflammation Tenosynovitis often accompanies the arthritis It involves especially the tendons around the ankles wrists and finger joints The skin over these tendons becomes swollen tense and hot and motion of any kind becomes unbearable because of the excruciating pain

Table 40 shows the frequency with which the individual joints were affected in our 200 patients with gonococcic arthritis The knees were more often involved than any other joints followed by the ankles and wrists although none were entirely exempt

Fever varies anywhere from none to 1 or 2 degrees in mild cases up to the severe septic types of fever which may reach 104° or 105° F in severely ill patients

Course

Many patients have a few intermittent aches or swollen joints for several days and then the infection is gone Other patients get well within a few weeks while in still others the infection tends to localize in a single joint where it remains active for months and often leaves considerable destruction in its wake Atrophy occurs in the muscles around joints which have been affected for long periods of time

Associated Infections

Other gonococcic complications may be associated with arthritis and tenosynovitis These include conjunctivitis (which is called catarrhal since gonococci cannot be found in the exudate) iritis panophthalmitis endocarditis meningitis myositis and localized abscesses

Laboratory Examinations

The Synovial Fluid This will provide valuable information if it is aspirated Myers[13] was able to cultivate gonococci from the synovial fluids in one fourth of his patients He felt that in the joints from which the organisms could not be cultured the inflammation was chiefly below the surface of the synovial membrane and in the periarticular tissues The leukocyte count of the synovial fluid varied from 1800 to 78 000 per cu mm in noninfected fluids and from 7100 to 158 000 in infected ones Polymorphonuclear leukocytes usually predominated comprising 46 to 100 per cent of the cells

vial fluid removed should be injected on alternate days until signs have disappeared and no further fluid can be aspirated from the joint

Other guides to therapy are the leukocyte count in the blood and synovial fluid the sedimentation rate and the disappearance of gonococci from the synovial fluid and from the local genitourinary lesion The intramuscular injections should be continued until the blood leukocyte count and the sedimentation rate have reached normal Cultures should be taken repeatedly from the urethra prostate and seminal vesicles in men and from the urethra cervix and Bartholin s

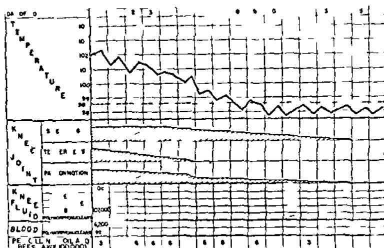


Fig 37 Temperature chart of a patient with gonococcic arthritis treated with penicillin.

Two months before admission the patient had a moderate amount of pain in the left wrist which disappeared without treatment after a few days. Four days before admission the patient had a chill followed by swelling pain and tenderness in the left knee and urethral discharge

The knee fluid was cloudy and had the characteristics shown in the figure Gonococci were seen on smear and grown on culture Penicillin was given in doses of 300 000 units twice a day Improvement began within forty-eight hours and was complete in two weeks A second specimen of synovial fluid obtained on the twelfth day of therapy showed no gonococci on smear or culture

glands in women and treatment should not be discontinued until the gonococci have disappeared from these foci The complement fixation test is of little value in assessing the results of treatment since it may never become positive in patients treated early in the disease or when it is positive it may remain so for weeks or months

In patients with the chronic form of the disease improvement is so gradual that it is often difficult to tell when to stop the administration of penicillin When all obvious evidences of infection have disappeared and when the leukocyte count and sedimentation rates

metastasis from some other focus of infection the location of which should aid in the differential diagnosis

Reiter s syndrome resembles gonococcic arthritis so closely that the two cannot be differentiated except by bacteriologic and serologic tests Urethritis conjunctivitis and multiple arthritis occur in both diseases Reiter s syndrome occurs almost exclusively in men Cultures of the urethral exudate do not contain gonococci and the gonococcic complement fixation test is negative

Rarer forms of joint disease which may be confused with gonococcic arthritis are syphilitic arthritis brucella arthritis shigella arthritis tuberculous arthritis the arthritis of rat bite fever gout hemorrhage into a joint as a manifestation of hemophilia and the arthritis which occurs as a complication of *Streptococcus viridans* endocarditis

Prognosis

It is impossible to predict how much time will be required for a particular patient to get well The acute infection may last from a few days to several weeks In the latter event a chronic process may continue for several weeks or months more The inflammation will gradually subside in every *case* but *will often leave residual changes* which will cause permanent disability Keefer[6] found that in patients who showed organisms in the synovial fluid and a cell count above 10 000 per cu mm the outlook was poor Only 37 per cent of his sixty nine patients recovered completely without residual signs of joint disease These patients were observed in presulfonamide days Since these drugs have been employed the prognosis is considerably better and it is to be expected that with the use of penicillin it will be better still

Treatment

Penicillin The effectiveness of penicillin in gonococcic arthritis cannot be predicted on theoretical grounds since on the one hand the organism is very susceptible to penicillin while on the other hand absorption of the antibiotic into the joint cavity is good only if large doses are given Originally we[8] tried doses of 25 000 units intramuscularly every four hours but although this amount of penicillin brought about the recovery of some patients others were not benefited We have therefore given higher doses to the patients treated more recently and now recommend intramuscular injections of 300 000 units of penicillin in oil and beeswax every twelve hours (Fig 37) or 100 000 units in aqueous solution every two hours With these doses we have not found it necessary to inject penicillin into the synovial cavity It is conceivable that it may be necessary to inject penicillin locally if the arthritis is grossly purulent In such cases all the fluid obtainable should first be removed and 50 000 units of penicillin dissolved in a volume of isotonic salt solution slightly less than the amount of syno-

Gonococcic Ophthalmia

The conjunctivae are among the membranes especially susceptible to the gonococcus. They may be infected in three ways: (1) by transmission through the medium of fingers, towels, washcloths and so on or from a person with a gonorrheal infection; (2) by the direct contact of a baby's eyes with the birth canal of an infected mother (*ophthalmia neonatorum*); and (3) by metastasis in a patient with gonococcic bacteremia. In the first group usually only one eye is affected. In the latter two groups it is most often bilateral.

Although *ophthalmia neonatorum* is not so common as it used to be before the days of compulsory instillation of silver salts into the eyes of all babies at birth, it is still frequently encountered and must be reckoned with as an important cause of blindness.

Symptoms and Signs

These vary all the way from a mild conjunctivitis in the metastatic form and in patients infected with a relatively avirulent organism to a severe fulminating panophthalmitis. The latter patients exhibit swelling, redness and tenderness of the lids and underlying structures with a sensation of smarting pain in the eye and an ache in the frontal and temporal regions. A purulent discharge follows which, in favorable cases, subsides within two or three weeks, leaving a chronic inflammation which lasts for several more weeks.

Complications

Corneal ulceration occurred in 25 to 30 per cent of patients treated in presulfonamide days. It was sometimes slight and sometimes severe enough to cause permanent blindness.

Prevention

Ophthalmia neonatorum may be prevented by instilling 2 drops of 1 per cent silver nitrate solution into the conjunctival sacs immediately after birth. In most states physicians are required by law to perform this service for every newborn child. Franklin[3] found penicillin as effective as silver nitrate in preventing gonococcic conjunctivitis. He used a solution of 2500 units of crystalline sodium penicillin per cubic centimeter of isotonic saline solution or distilled water. One drop of the penicillin solution was instilled in the conjunctival sac of each eye within the first hour after birth and at daily intervals for the next three days. If these results are confirmed, penicillin should be preferable to silver nitrate for prophylaxis, since the latter often causes a considerable amount of local irritation.

are normal and gonococci can no longer be cultured from any focus we consider it best to give the intramuscular injections for one more week and then discontinue them

In general the larger the doses of penicillin and the longer the treatment is continued the better the results Among eighteen patients to whom we gave a total dose of less than two million units of penicillin only six recovered whereas among the twelve patients who received more than two million units ten recovered

Sulfonamides Formerly excellent results followed the use of sulfonamides in gonococcic arthritis Coggeshall[1] and Keefer[6] using sulfanilamide found that if the concentration of the drug in the synovial fluid was sufficiently high the gonococcic infection could almost always be eradicated Later sulfathiazole and sulfadiazine took the place of sulfanilamide and the results were even better

Among 140 patients with proved gonococcic arthritis who were treated with sulfonamides at the Gallinger Municipal Hospital ninety eight (67 per cent) recovered The best results were obtained in the early years of sulfonamide therapy In recent years the recovery rate has dropped to 50 per cent apparently due to the increasing prevalence of sulfonamide resistant strains

In spite of the appearance of sulfonamide-resistant gonococci however many patients still recover during sulfonamide therapy For this reason we believe that sulfonamides have a place in the treatment of gonococcic arthritis and should be employed in any case where improvement does not occur after large doses of penicillin have been given

Fever Treatment This has been discussed on page 233 An occasional patient may not respond either to penicillin or the sulfonamides and may need fever treatment as a last resort Treatment in a fever cabinet is superior to fever induced by typhoid vaccine in our experience We observed recovery in 64 per cent of thirty three patients treated by the former method while only 45 per cent of twenty two patients recovered after receiving typhoid vaccine

Symptomatic Treatment During the interval necessary for penicillin or sulfonamides to take effect the patient should be made as comfortable as possible Salicylates often give considerable relief from pain If they are unsuccessful in this codeine or morphine may be used

Complete rest of an acutely inflamed joint will help considerably to relieve pain This may be obtained by the use of splints sandbags or by a half shell cast The orthopedic surgeon should be called to help if relief cannot be obtained by the use of simple measures His services are invaluable also in preventing deformities and ankyloses and in treating these conditions when they have developed

Preexisting valvular disease is not necessary for the implantation of gonococci on heart valves and is present in only a fraction of the cases. The individual valves involved are listed by Stone[4] as they were found in 108 cases

Aortic	[illegible]	Aortic and tricuspid	1
Mitral	30	Aortic tricuspid and pulmonary	1
Pulmonary	1	Mitral and tricuspid	2
Tricuspid	1	All four valves	1
Aortic and mitral	8		

It will be seen that right-sided involvement although not encountered so frequently as left sided implantations was more frequently observed than in many other types of endocarditis

Petechiae and embolic phenomena occur almost as frequently as in *Streptococcus viridans* endocarditis The lungs are particularly likely to be the site of infected emboli due to the frequency of involvement of the right side of the heart These infarctions are often followed by pneumonia or pleurisy Emboli frequently lodge in the brain kidneys spleen and peripheral arteries Arthritis is of course much more common than in endocarditis caused by other bacteria Other associated conditions are pericarditis nephritis conjunctivitis and meningitis

Laboratory Examinations

Leukocytosis is present in practically every case together with an increase in the percentage and a shift to the left of the granulocytic cells Repeated blood cultures should be taken in every instance They are positive in a fairly high percentage of patients when this is done A positive culture for gonococci from the genitourinary tract or a positive blood complement fixation test is presumptive although not definite evidence that the endocarditis is gonococcic

Diagnosis

Endocarditis should be suspected whenever the temperature is higher and the signs of toxicity are more pronounced than would be expected from gonorrhea itself or from an associated arthritis if this is present If valvular murmurs appear or increase in intensity or if petechiae or embolic phenomena are present the likelihood of endocarditis becomes more certain

Whenever endocarditis is diagnosed the gonococcus should be suspected as an etiologic factor and the genitourinary system investigated by history and bacteriologic examination of discharges cervical smears or the material obtained from prostatic massage

Prognosis

Although several cases were observed in which recovery occurred nearly every patient with this disease died during the era before penic

TREATMENT

Sulfathiazole and sulfadiazine have been found to be most efficient among the sulfonamides An initial dose of 0 03 gm (½ grain) per pound of weight should be given to children followed by four hour doses totaling 0 06 gm (1 grain) per pound of body weight for each twenty four hour period Adults should receive 4 to 6 gm (60 to 90 grains) initially followed by 1 gm (15 grains) every four hours This regimen should be continued until the clinical signs have disappeared and smears and cultures from the eyes have become negative In three fourths of the patients the bacteria disappear within three days while in practically all patients they are absent by the end of the second week Corneal ulcerations are infrequent and the resulting scars if they occur at all are much smaller in sulfonamide treated patients than in those treated by previous methods

Penicillin shows great promise in this disease as in other gonococcic infections Rapid recovery occurred in all the thirty patients treated by Lewis[10] He administered penicillin intramuscularly at three hour intervals in doses of 20 000 units for adults 10 000 units for children and 5000 units for infants The average period of hospitalization in penicillin treated patients was 4 6 days compared with 5 7 days for those who received sulfadiazine and 20 3 days for patients treated in the presulfonamide era Sorsby[19] has reported excellent results from the conjunctival instillation of a physiologic salt solution containing 2500 units *of penicillin per cubic centimeter Further studies* will be necessary before the relative value of penicillin and sulfonamides and of systemic versus local penicillin treatment can be determined

Little local treatment is needed The affected eye should be washed by instilling into the conjunctival sac several drops of boric acid or isotonic saline solution at two hour intervals until pus is no longer present Care must be exercised to prevent the well eye from becoming infected Infants should be placed with the affected eye lowermost Older patients may need shields or bandages on the uninvolved eye for this purpose

Gonococcic Endocarditis

SYMPTOMS AND SIGNS

This dreaded complication may have its onset anywhere from one to six weeks after the beginning of the genitourinary infection and sometimes even later It may begin suddenly with chills high fever and general toxicity or may arise unnoticed while attention is directed to the original infection or to arthritis

Fever is the most prominent manifestation and the temperature characteristically goes as high as 105° F each day In an occasional patient it rises twice during each twenty four hour period Chills are present at some time in the course in about half of the patients

in a woman or child with concomitant or recent gonorrhea. It is confirmed by finding the gonococci in smear and culture.

Treatment is with penicillin. A larger amount should be administered than when a genitourinary infection exists alone. From present indications 250 000 to 300 000 units divided into five equal doses and given intramuscularly at two- or three-hour intervals should be sufficient.

Other Manifestations of Gonococcic Infection

Cutaneous Manifestations

These include simple erythema, urticaria, erythema nodosum, petechial, hemorrhagic and bullous exanthems and a hyperkeratotic type of dermatitis. The latter is the only typical skin lesion associated with gonococcic infections and is called *keratodermia blennorrhagicum*. It consists of crust-covered papules which occur in association with a local gonococcic infection and gonococcic arthritis. It is especially important for the clinician to be aware of these varied dermatologic manifestations of gonococcic infections since many of them can be confused with the rashes caused by the sulfonamides. Recovery has been reported after treatment with penicillin.

Nephritis

Pyelonephritis and pyelonephrosis are uncommon and true glomerulonephritis is rarer still. When they occur they follow the course of similar infections caused by other bacteria.

Other Infections

Other infections caused by gonococci are myositis, localized abscesses, pneumonia, pleurisy, pericarditis and thrombophlebitis. All should be treated with large doses of penicillin.

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illin therapy was employed after a course lasting from one to five months

TREATMENT

As soon as the diagnosis is established penicillin should be given While the gonococcus is among the organisms quite susceptible to this antibiotic the frequency with which multiple complications occur and the rapidly progressive course require the employment of large doses *Whenever possible the sensitivity to penicillin of the gonococcus* (obtained from the blood or elsewhere) should be tested and considered in the decision as to the doses to be employed The reader is referred to the section on *Streptococcus viridans* endocarditis for details of this treatment (p 179) Although only a few patients with gonococcic endocarditis have been treated up to the present time it is to be expected that many will recover if the proper treatment is given

Gonococcic Meningitis

The meninges are infrequently involved in the course of generalized gonococcic infections Rarely gonococcic meningitis occurs without evidence of coincident or preceding genitourinary infection In these cases the clinical manifestations are similar to those of meningococcic meningitis and a distinction cannot be made between the two except by the fermentation reactions of the organisms cultured from the spinal fluid

Treatment is with sulfadiazine combined with the employment of penicillin for the purpose of attacking the bacteria at the original site of infection Since the regimen to be followed is the same as that used in meningococcic meningitis the reader is referred to that section (p 217) We have observed a case of primary gonococcic meningitis in which recovery occurred promptly after the use of sulfadiazine and believe that the prognosis should be as good as in meningococcic meningitis if the proper treatment is carried out

Gonococcic Proctitis

In the female gonorrhea often spreads to the anus and rectum where it usually affects only the superficial layers of the mucous membranes although it may spread to the deeper structures and remain pocketed there for weeks or months The focus in the rectum may reinfect the cervix and urethra

Among the *symptoms and signs* are sensations of irritation at the anus and of fullness within the rectum constant aching pain which may radiate to the abdomen sacrum or thighs pain on defecation yellowish rectal discharge and blood in the stools

The *diagnosis* may be suspected when a purulent proctitis is found

Part III

DISEASES CAUSED BY BACILLI

13 *Eberthella Infections (Typhoid Fever)*

Eberthella typhosa is a short fat gram negative flagellated motile bacillus The disease for which it is responsible typhoid fever has long afflicted man It was universal before the early 1900 s when water and food supplies were not guarded from contamination Even today under circumstances or in places where vigilance is not maintained it breaks forth in all its former fury This is particularly true in rural areas in countries where the people are too poor or too ignorant to observe the laws of sanitation or during the mass migrations incident to wars But though typhoid fever is no longer the scourge of yester year let it not be thought that it is insignificant today Hundreds and thousands of carriers persons who for the most part had the disease and recovered from it months or years ago roam at large in our society excreting the bacilli in stools or urine If these people contaminate food or other objects which are transmitted to the mouth of someone else that person is almost always stricken with the disease Such cases are often sporadic and consequently much harder to diagnose than when they occur in epidemics because the infection is not sus pected Moreover since sporadic cases may escape detection for a longer period the patient s attendants run a greater risk of contracting the disease By one means or another over 5000 persons in the United States became ill with this disea e during 1944 and 501 persons died from it Typhoid fever therefore although less conspicuous today than formerly presents an even greater challenge if we are to diagnose each case properly prevent its spread and eventually stamp it out altogether

When a sufficient number of *Eberthellae* gain access to the gastro intestinal tract of an individual they penetrate the intestinal wall and settle in the solitary and aggregated lymphatic nodules (Peyer s patches) of the intestines If the individual s immunity does not effec tively localize the bacilli and prevent their growth the organisms spill over into the blood and continue to do so until the patient develops sufficient immunity to confine them once again to the lymph tissues of the intestinal wall and to the lymphatic structures elsewhere in the body such as the spleen the liver the bone marrow and the lymph

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24 Warren C F Hinton W A and Bauer W Significance of Gonococcus Complement Fixation Test as a Diagnostic Aid in the Study of Arthritis J A M A *108* 1241 1937

The patient is quite dull and heedless of his surroundings. Emaciation becomes apparent toward the end of this period and muttering delirium and muscular twitching appear in severe cases.

During the third or fourth week convalescence commonly begins. The temperature declines gradually during another week or more. Rarely it drops by crisis. A low grade fever may persist for some time or *there may be another rise in temperature* with or without reappearance of the other features of the disease. Hypothermia may be present for several days or a week or two after the temperature falls. The patient's interest in food and in his surroundings returns and along with this his strength but it is a month or more before he is able to resume his customary activities.

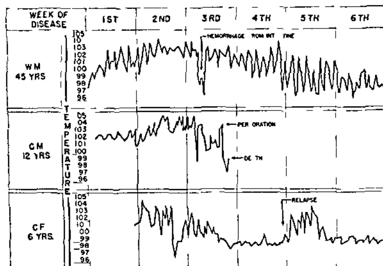


Fig. 38. Temperature charts of three patients with typhoid fever showing the complications of hemorrhage, perforation and relapse.

Chills are usually seen only at the onset or during the period of rising fever although some patients experience them throughout the disease. Procedures which cause a decided decrease in the temperature such as cold baths or the administration of antipyretic drugs may be followed by a chill. A chill may also herald the onset of a complication such as hemorrhage, perforation, pneumonia, relapse or the establishment of a secondary focus.

Eruption. The typical rash of typhoid fever is composed of round slightly raised flattened papules about 2 to 5 mm in diameter called rose spots. They are pale red at first turning somewhat darker later. Occasionally they may be purpuric. The rose spots may appear at any time during the disease coming out in one or several successive crops

nodes They continue to pour out endotoxins until the patient succumbs to or recovers from the disease All this time the bacilli are causing local destruction of the lymphatic structures of the intestinal wall with consequent ulceration in many areas and the attendant danger of perforation into the peritoneal cavity This latter possibility is an ever imminent peril through the entire course of the disease and well into convalescence until the ulcers are healed

Typhoid fever is found most frequently in the second third and fourth decades of life This age distribution is probably accounted for by the greater possibility of exposure of persons at these ages Furthermore in areas where the disease is endemic most people have acquired some degree of resistance by the time they are forty years old

Symptoms and Signs

In presenting the clinical manifestations of typhoid fever we shall refer freely throughout this chapter to the 1500 cases analyzed by McCrae[10] The incubation period varies from three days to three weeks or more It can seldom be determined accurately because of the gradual onset The patient usually experiences headaches malaise and anorexia for several days before he takes to his bed Less often he complains of cough vomiting chilly sensations diarrhea or constipation during this early period The disease occasionally begins abruptly with a chill (in 22 per cent of 1500 cases) or epistaxis (in 20 per cent)

The course of a typical case of the disease consists in a period of gradually rising temperature during the first week a period of continued fever which is called the fastigium and which lasts about two weeks and then an interval of one or more weeks of descending temperature In Figure 38 the first temperature curve illustrates the period of ascending fever followed by the fastigium (which in this case was interrupted by a temporary drop in the temperature due to hemorrhage) and then by the period of descending fever

The first period of fever is classically described as a gradual steplike ascent each evening's temperature being higher than that of the evening before While this is the picture seen in many cases it is by no means universal The rise in fever may take place in an irregular manner over a period of several days or the temperature may reach its maximum within a few days and remain there During the period of increasing fever the patient becomes more toxic Sluggishness of the mental faculties and short periods of mental confusion appear especially when the temperature becomes high

In the typical case the plateau of fever begins during the second week and lasts for a week or two The temperature remains in the neighborhood of 102 to 105° or even 106° F with little variation during each day In occasional patients the temperature is irregular during these weeks Rarely it is intermittent and suggests malaria

in size but usually remains fairly soft It is sometimes tender although seldom painful The swelling subsides as the temperature returns to normal

Respiratory System Because the physician associates typhoid fever with intestinal lesions and generalized bacteremia he is likely to forget that over one-fourth of these patients have a cough as a result of bronchial involvement Consequently he may misdiagnose their condition as influenza bronchitis or pneumonia rather than typhoid fever The bronchitis in typhoid fever is characterized by a cough productive of a small amount of mucoid sputum and numerous rales over the region of the large bronchi and sometimes throughout the chest Occasionally small amounts of blood are coughed up The bronchitis is usually not serious and disappears as the temperature falls and often before Pneumonia will be considered under complications

Cardiovascular System A most characteristic feature is the relative bradycardia the heart rate being ten to thirty beats less per minute than would be expected from the height of the fever Bradycardia is present during the early part of the disease in most patients and is observed throughout the entire course in a great many The heart rate may become rapid in patients who are seriously ill and in those with intestinal hemorrhage or perforation A dicrotic pulse is present as a rule in adults during the first half of the disease It is not found so frequently in children or in adults during the second half of the disease Porter[14] has shown that the heart is not usually enlarged in typhoid fever and that murmurs and congestive heart failure are not characteristic of the disease He found electrocardiographic abnormalities in fourteen out of thirty patients and Brow[2] found them in fifteen out of sixty five These consisted of lengthening of the PR interval in most instances and in occasional cases of T wave changes These abnormalities appeared as early as the ninth day of the disease and as late as the forty fourth day They usually lasted only a few days and disappeared eventually in every patient who recovered They are probably accounted for by the multiple endarteritic and periarteritic changes which have been demonstrated in the coronary vessels in typhoid fever Their presence has no relationship to the severity of the disease and they cannot be shown to have any direct bearing on the outcome

The blood pressure especially the diastolic pressure is usually low throughout the course of typhoid A sudden fall below the customary levels may be the earliest and most reliable sign of intestinal hemorrhage

Nervous System Dull headaches are frequently complained of during the first week or two In an occasional patient they are very intense They disappear or are unnoticed during the stuporous period which follows Insomnia also may be present early but is usually

and lasting three to five days Less frequently they may be present only a day or part of a day Often there are only six to ten present at a time Rarely they may pepper the trunk completely While the most common location for them is the abdomen and lower chest they may appear on the back on the neck and face or on the upper or lower extremities alone or in combination with other sites In 1500 cases they were observed in 93 per cent of the white patients while they were detected in only 21 per cent of the Negro patients

Gastrointestinal System This is usually affected although not in the same way in every patient The tongue becomes dry heavily furred and its surface fissured and somewhat cracked The lips are dry and cracked and may bleed The breath is foul and unless the mouth is cared for assiduously complications such as infection or ulcerations of the mucous membrane or parotitis may supervene The appetite usually diminishes soon after the onset and returns as the fever falls or sometimes several days sooner It is important to emphasize however that the patient seldom refuses food fed to him with patience and a little coaxing

Constipation is the most frequent gastrointestinal symptom It was present in 51 per cent of 1500 patients Diarrhea was present in 17 per cent of the patients This latter condition makes for a poor prognosis since it usually indicates extensive ulceration in the colon Although in most instances there were only three to five stools per day in a few patients more severe diarrhea occurred

Abdominal distention is a troublesome complication which is present to some degree and at some time in nearly every patient If it is severe it produces a rise in the temperature and pulse rate and is often responsible for a considerable amount of respiratory embarrassment by pressure upon the diaphragm Since treatment is more effective when begun before the distention becomes severe early recognition is important The physician may often detect its first appearance by listening with the stethoscope and hearing a diminution in the normal peristaltic sounds

More than half of the patients have abdominal pain or tenderness or both at some time during the course of the disease The pain and tenderness may occur in any part of the abdomen and may be of any degree of severity Sometimes the onset of the pain is so sudden and its character so severe that it simulates acute appendicitis or gall bladder colic While the abdominal pain is due to distention or to pronounced peristaltic contraction in most instances it cannot be ignored because it may signify hemorrhage from or perforation of the intestine or other grave disorders These will be discussed under complications

During the height of the disease when the lymphoid tissue is universally invaded the spleen is likewise involved It increases moderately

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succeeded by drowsiness as the disease goes into its severest phase Meningismus is often present Partial deafness may appear as the disease becomes severe only to disappear completely during convalescence

During the course of the disease the victim's mind becomes progressively more clouded he appears apathetic and drowsy and although he can usually be aroused in order to eat or may even take part in a rational conversation he soon sinks back into his lethargy and may remember nothing that has been said or done even a few minutes before More severely ill patients lie in stupor for days paying no attention to their surroundings at all Particularly unwelcome to the attending physician is the appearance of *coma vigil* a state in which the patient is unaware of his surroundings although his eyes remain open and may even follow the movements of attendants about the room The patient may lie quietly mutter incessantly or may talk wildly the content of his talk being complete nonsense most of the time

Psychoses occasionally occur at the onset of the disease A confused or maniacal state may be the first evidence that something is wrong More frequently psychoses are present during the height of the fever Less often they may appear during convalescence Delirium is not uncommon delusions or hallucinations may occur and rarely hysteria may be observed Psychoses occurring at any of these stages may be expected to clear up completely although they may take weeks or even months to do so

CLINICAL FEATURES IN SPECIAL GROUPS

In children typhoid fever more often begins abruptly and runs a shorter course than in adults Abdominal pain at the onset is frequent while hemorrhage is rare and perforations are uncommon On the other hand neurologic symptoms are much more often observed than in adults

In the aged the onset is most often insidious the course is prolonged and termination of the fever and convalescence are gradual As a rule the symptoms are not typical Fever may be low and irregular abdominal symptoms mild or absent and stupor more pronounced and more prolonged than in young patients Thromboses of the peripheral veins and pulmonary complications (pulmonary congestion bronchitis and pneumonia) are more frequent in older patients

In the Vaccinated It is now a common practice to vaccinate persons likely to be exposed to typhoid fever These include soldiers doctors nurses and persons living in or visiting rural or tropical areas There is no doubt that antityphoid vaccination confers a certain amount of protection against typhoid fever Callender[2] states that after the compulsory administration of typhoid vaccine to the personnel of the

United States Army morbidity rates for typhoid and paratyphoid fevers decreased from about 25 per thousand annually in 1910 to below 0.2 per thousand in 1912. He reports a water borne outbreak in Hawaii in which five times as many nonimmunized as immunized persons developed the disease. Once the disease is contracted, however, its course and clinical characteristics, although milder in many instances, seem to be similar in general to those occurring in nonimmunized patients.

Laboratory Examinations

Eberthella typhosa can be isolated from the blood, feces, urine, bile and the rose spots. For purposes of diagnosis, culturing the first three of these materials is worth while. During the course of the disease there are periods when the likelihood of success with each type of specimen is particularly good. It is important to take advantage of this since positive cultures are much more valuable in the diagnosis than positive agglutination tests.

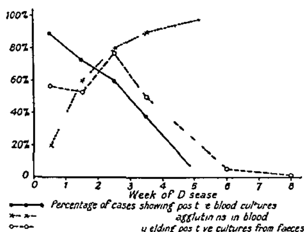


Fig. 39. Chart showing the incidence of positive blood and feces cultures and of blood agglutinins in typhoid fever in relation to the duration of the disease. (From Topley and Wilson, Principles of Bacteriology and Immunology, Edward Arnold & Company, London, England.)

Blood and Bone Marrow Cultures. Since typhoid fever is essentially a bacteremia, the diagnosis is made with most certainty if the organisms are cultured from the blood. As shown in Figure 39, the bacilli can be cultured from the blood in 90 per cent of patients in the first week of the disease. The proportion of patients with positive blood cultures decreases each succeeding week until it reaches approximately 40 per cent during the fourth week. Even after that time blood cultures may be positive in an occasional patient.

A method of obtaining the typhoid bacilli which is at present little used but which shows great promise and deserves to be employed more often is culture of the sternal bone marrow Ling[7] cultured eberthella or salmonella organisms from the bone marrow in forty four instances when parallel blood cultures were negative while blood cultures were positive concomitant with negative medullocultures in only two instances

Cultures from Feces Next in value for purposes of diagnosis is the isolation of the causative organisms in the stools These are positive in nearly 60 per cent of patients in the first and second weeks of the disease and in about 80 per cent during the third week Thereafter the incidence of positive stool cultures decreases throughout the course of the disease until after the sixth week the organisms seldom remain in the feces

Urine Cultures Typhoid bacilli are cultured from the urine less often than from the stools Like stool cultures however urine cultures are most frequently positive in the third week of the disease

Agglutination Test The patient responds to infection with the typhoid bacillus by the formation of agglutinins As shown in Figure 39 they can be found as early as the first week of the disease in 20 per cent of patients Thereafter the incidence rises progressively to reach 90 per cent in the fourth week and practically 100 per cent later The agglutination tests are carried out against two principal antigens of the typhoid bacillus the H or flagellar antigen and the O or somatic antigen The serums of vaccinated persons are characterized by a persistence of H rather than O agglutinins whereas the production of both types of antibodies occurs in the presence of the disease itself A more recently discovered component of *Eberthella typhosa* is associated with the property of virulence for mice and is called Vi antigen

The titer of H or O agglutinins may be as high as 1 5120 or more or may rise no higher than 1 40 during the disease Vi antigen titers reach 1 10 to 1 320

Many attempts have been made to determine an agglutinin titer which will invariably indicate that typhoid fever is present In our experience it is impossible to set a definite figure which would have this significance for several reasons

First although vaccination causes a rise in the titer of H agglutinins especially it usually produces some elevation of the O agglutinins and the Vi agglutinins also Second agglutinin titers to *Eberthella typhosa* may arise as an anamnestic reaction during the course of infections caused by other organisms especially those of the salmonella group A titer of 1 2560 is sometimes observed in patients with diseases other than typhoid fever especially if they have previously been immunized against typhoid Third agglutination tests as carried out in different laboratories vary considerably with regard to the antigens used and

the skill employed in reading the results. The very fact that these tests are simple to perform means that poorly trained technicians may often be assigned to do them. Accordingly, a single agglutinin titer, no matter how high, in itself can never be depended upon to make the diagnosis of typhoid fever. The titer of O agglutinins, or of both O and H agglutinins, which rises during a week or more of observation *is much more significant*, and is unlikely to represent an anamnestic reaction. Though titers do not always rise steadily during *the course of typhoid fever, an increasing titer* affords the strongest diagnostic evidence obtainable by serological study. Sometimes, particularly *in previously vaccinated individuals, the titers fluctuate irregularly*.

Blood Cells. *The leukocyte count is usually within normal limits* during the first week or two and later is characteristically below 5000. *In some cases it may remain within the normal range throughout the* disease. It is rarely above 10,000 per cu. mm. unless complications are present. *Leukocytosis may be caused by three groups of complications*: (1) hemorrhage from or perforation of the intestine; (2) complications of the disease elsewhere in the body, such as pneumonia, phlebitis, cholecystitis; and (3) unrelated infections, such as furuncles and abscesses.

The differential count shows a diminution in the number of neutrophils and a relative increase in the lymphocytes, particularly during the second and third weeks. The proportion of monocytes is frequently increased, in some instances up to 15 per cent. One feature that may be of diagnostic importance is the complete, or almost complete, absence of eosinophils.

By the time the disease is a few weeks old an anemia has also appeared. Stuart[18] found that at its lowest point, at the end of the third week, the red blood cell count averaged 3,200,000 per cu. mm. After this it started to rise and reached normal levels during the sixth week.

COMPLICATIONS

Intestinal Hemorrhage. Hemorrhage is the most frequent of the serious complications of typhoid fever. It was observed in 7 per cent of 1500 cases. Hemorrhages are the result of the erosion of one or more blood vessels in ulcerated areas. *Small clots frequently seen in the* stools of many typhoid patients are not important and are not usually *spoken of as indicating hemorrhages.* Small hemorrhages which may occur during the earlier weeks of the disease are rarely serious.

From the end of the second week on, however, the patient may at any time lose blood from the bowel in an amount varying from a few *cubic centimeters to a liter or more. The hemorrhage* usually comes on suddenly. The onset may be symptomless or may be accompanied by a mild *or occasionally a severe abdominal pain.* Depending upon

the previous state of the patient and the amount of blood lost the effect on the victim varies from no observable change to a severe state of shock with subnormal temperature a cold skin covered with sweat lowered blood pressure and a fast feeble pulse The first graph in Figure 38 illustrates a case in which hemorrhage was accompanied by a transient fall in the temperature The stool containing the blood is usually liquid and reddish in color Sometimes it contains both fluid and clotted blood Occasionally only dark clots are present Hemorrhages may occur repeatedly at varying intervals through the course of the disease and even well into the period of convalescence No definite predisposing causes have been established and except for insistence upon quiet for the patient and upon his following the proper dietary regimen no preventive measures are known

Intestinal Perforation As stated before the *Eberthellae* early gain a bridgehead in the lymphatic tissue of the intestinal wall and remain there throughout the disease The patches of lymph tissue become hyperemic and swollen They then become necrotic and part of or all the tissue in the patch sloughs away to leave an ulcer From that time until the ulcer heals there is constant danger that it will perforate and allow the intestinal contents to enter the abdominal cavity This is the most dreaded complication of typhoid fever It occurred in 2 6 per cent of 1500 patients Among thirty eight patients ten were affected during the second week twelve during the third week seven during the fourth five during the fifth one during the sixth two during the seventh and one during the eighth week

The symptoms of perforation are abdominal pain nausea and vomiting increasing toxicity sweating and signs of circulatory collapse The onset is most often sudden with sharp intense abdominal pain In delirious or stuporous patients the presence of the pain may be suspected if they become extremely restless The pain characteristically returns in paroxysms which come at intervals and as a rule do not last long Although the site varies it is usually in the lower abdomen Sometimes the pain is referred from the diaphragm along the phrenic nerve to the neck or it may be referred to the genitalia Along with the pain there is almost invariably a pronounced degree of tenderness on palpation This may be generalized over the abdomen or localized in one spot Rigidity and muscle spasm are also present although often they can be detected only during the time when the pains are present

The course of the temperature pulse and respiration after perforation is variable The temperature may rise fall or be elevated for a short time only to drop later The pulse and respiratory rates are usually increased Nausea vomiting and hiccup occasionally occur If the perforation is not diagnosed and the patient is not operated upon general peritonitis will supervene This is characterized by a pinched anxious expression pallor cyanosis cold sweating skin and

a rapid feeble pulse Vomiting is often present and occasionally hiccup The abdomen becomes increasingly more distended and peristaltic sounds diminish and cease altogether

The most important laboratory examination is the leukocyte count Here the careful clinician should reap the benefit of the blood counts which were done repeatedly during the uneventful and monotonous days or weeks which preceded These form a base line which enables him to judge the significance of any slight rise When a perforation is suspected hourly leukocyte counts should be done In most cases there is a steady rise beginning immediately or within a few hours after the perforation occurs Occasionally there is a rise followed by a fall or even a decided drop in the count from the onset A roentgenogram of the abdomen gives unequivocal proof of a perforation if it shows the presence of free air beneath the diaphragm

Other complications which may simulate perforation are (1) Appendicitis rupture of a suppurating lymph node or peritonitis from other causes such as direct extension from an ulcer without perforation Their differentiation is not important since all these conditions call for immediate operation (2) Abdominal pain from distention or constipation This pain is not so severe as the typical pain of perforation and when observed for a period of time is not accompanied by the other features of perforation (3) Intestinal hemorrhage This is only rarely accompanied by rigidity and muscle spasm Furthermore it causes a drop in blood pressure and hemoglobin (4) Phlebitis of the iliac vein This may confuse the clinician until a careful examination is done (5) Acute cholecystitis (see page 264)

Phlebothrombosis and Thrombophlebitis Venous thrombosis was diagnosed in 2 7 per cent of 1500 patients As would be expected in persons who are confined to bed for so long a time and who often lie for hours in a stupor patients with typhoid fever are likely to develop simple thrombosis (phlebothrombosis) in the veins especially in those of the lower extremities Pain in the affected leg may draw attention to this condition or tenderness may be discovered on routine examination Pulmonary embolism or edema of the affected limb sometimes occurs Fever appears late if at all

A smaller percentage of typhoid patients develop actual thrombophlebitis often with a chill at the onset followed by fever swelling and pain in the affected extremity and by tenderness along the course of the affected vein These patients usually exhibit leukocytosis with a relative increase in the neutrophils

Pneumonia occurred in 1 5 per cent of 1500 patients It would undoubtedly be detected more often than this if chest roentgenograms were taken routinely This complication may be caused by pneumococci or it may be a mixed infection caused by the bacteria ordinarily present in the bronchi Occasionally it is due to the typhoid bacillus itself

If the etiologic agent is a pneumococcus the clinical picture is similar to that of any pneumococcic pneumonia often with chills at the onset pleural pain rusty or blood tinged sputum high fever and leukocytosis The prognosis is worse than when either disease occurs alone A mixed infection is likely to occur in a patient who is greatly debilitated as a result of typhoid fever Accordingly its outcome depends largely upon the general condition of the patient Pneumonia due to *Eberthella typhosa* itself represents a serious infection

Cholecystitis During the bacteremic stage the *Eberthellae* lodge in the gallbladder Here they may produce no inflammation at all or they may cause cholecystitis of any severity with or without the formation of calculi Cholecystitis was observed in 1 5 per cent of *1500 patients* The characteristic features of the attack are pain in the region of the gallbladder nausea vomiting and fever occasionally accompanied by a chill Tenderness and muscle spasm can be elicited in the right upper quadrant of the abdomen Jaundice is sometimes present leukocytosis often The attack usually subsides after several days although it may go on to perforation

Instead of causing an attack during the course of the typhoid fever the infection more commonly remains dormant and later produces chronic cholecystitis and cholelithiasis

Other Complications Less frequently there occur abscesses in the skin subcutaneous tissues and bones osteomyelitis abscesses and gangrene of the lungs pleurisy empyema peritonitis hemorrhage from or perforation of the stomach hepatitis pyelitis nephritis arterial thrombosis neuritis and meningitis Most of these are seen less frequently now than in the past chiefly because of the newer knowledge *of nutrition and better nursing care*

Relapse and Recurrence

Relapse is frequent in typhoid fever In about 10 per cent of patients, after the temperature has reached and remained within approximately normal limits for a period varying from one day to six weeks there is a second rise in the temperature although no complications or associated diseases can be found to explain it (See the third temperature chart in Figure 38) When this secondary fever is accompanied by one or more of the features of typhoid fever the episode is termed a relapse When there are no signs and symptoms except malaise and headache accompanying the fever the episode is called a recrudescence The difference is probably only quantitative however In either case there is undoubtedly a shift in the balance between the resistance of the patient and the ability of the organism to invade and multiply During the period of normal temperature the host has obtained the upper hand When fever recurs the organisms have regained some degree of dominance If the degree is small there may be elevation

of fever for a few days to two or three weeks accompanied only by malaise and headaches in other words a recrudescence If the dominance of bacteria over the host is more pronounced other features of the disease will be present such as rose spots enlargement of the spleen bacteremia and an elevation of the agglutinin titer In rare instances there may be two or more relapses Although occasional relapses may be quite severe some of them ending fatally the prognosis in most cases is much better than for an initial attack A condition in which the temperature is falling but has not yet reached normal and suddenly rises again and is accompanied by increased signs and symptoms of the disease is called an intercurrent relapse These relapses tend to be more prolonged more severe and more often fatal than the ordinary relapses

Recurrence Although persons who have recovered from typhoid fever usually retain a considerable degree of immunity for years and perhaps for life their defense is not impregnable and may be overwhelmed by large numbers of virulent organisms Such cases are rare but they undoubtedly occur In other patients an apparent recurrence of typhoid fever can be explained by the fact that either the first or the second attack was due to paratyphoid bacilli (see chapter on Salmonella Infections)

Diagnosis

There is no single clinical feature which is invariably present and no laboratory test which is always positive in typhoid fever Consequently the ability to diagnose this disease calls for skill in marshalling the pertinent facts and astuteness in judging their relative importance Whenever a patient has fever without definite localizing signs to explain its origin typhoid must be considered If drowsiness and apathy relative bradycardia gastrointestinal symptoms (which may be pain constipation or diarrhea and need not be pronounced) are present the physician may be highly suspicious of typhoid Rose spots or an enlarged spleen offer excellent corroborative evidence and a history of recent residence in an area of endemic typhoid makes the diagnosis still more certain

The laboratory is often needed to make the diagnosis and should always be called upon to confirm it If the patient is seen during the first two or three weeks of the disease the blood culture is likely to be positive When repeated blood cultures are taken the chances of obtaining the organism are nearly 100 per cent Cultures of the stools will be almost as helpful during this stage Agglutination tests for both O and H agglutinins should be made for comparison against later tests done at weekly or ten day intervals Vi agglutination tests are not run as a routine by most laboratories and their significance in diagnosis is doubtful Later stool and urine cultures and agglutinins

give the most aid but it is always good policy to obtain a blood culture also even when the patient is first seen late in the disease

Differential Diagnosis Other diseases characterized by continued or irregular fever with few or no localizing symptoms and signs are acute miliary tuberculosis bacterial endocarditis malaria and brucellosis The first of these may show all the characteristics of typhoid fever except the rash Helpful differential points are a history of previous tuberculosis or of contact with a patient suffering from this disease alertness and a feeling of well being instead of the usual apathy of typhoid fever the appearance of miliary tubercles in the choroid and the characteristic appearance of the roentgenogram of the lungs It must be remembered however that often these last do not appear until six or eight weeks after the onset of the disease so that one normal roentgenogram should not be taken as final

In most cases of bacterial endocarditis the fever is somewhat lower than in typhoid and almost always a heart murmur appears or a change takes place in a preexisting murmur Petechiae subcutaneous nodules and hematuria are likely to occur Blood cultures will show a streptococcus a staphylococcus or a pneumococcus in the majority of cases while the stools will not of course contain typhoid bacilli

Although an intermittent fever is the rule in malaria high irregular and even continuous fevers are sometimes seen Leukopenia and enlargement of the spleen are present as in typhoid Repeated chills are frequent in malaria rare in typhoid Assiduous searching of the blood films for the malarial parasites will sooner or later establish the true diagnosis Meanwhile blood and stool cultures should be taken to make sure that the patient does not have typhoid

Brucellosis or undulant fever is similar to typhoid in that the bacteria gain access through the intestinal tract and produce a bacteremia and a long standing infection Clinically the picture is often exactly like that of typhoid The blood cultures agglutination tests or skin tests or a combination of these should be positive in undulant fever

Influenza often presents diagnostic difficulties especially if it is severe It is frequently found in other members of the family or in other contacts and is usually accompanied by some symptoms of upper respiratory disease Its diagnosis depends upon the exclusion of other diseases as the cause of the fever since there is no laboratory test in routine use for the diagnosis of influenza

Weil s disease may be difficult to differentiate before the jaundice appears Severe muscular aching conjunctival injection and leukocytosis point to Weil s disease and the *Leptospira icterohemorrhagiae* can be recovered from the blood and urine by inoculation into guinea pigs and mice Later agglutinins develop against the *Leptospira*

Typhus fever is easily confused with typhoid before the rash appears

Even after the exanthem is present it may simulate typhoid. The onset of typhus fever is usually more abrupt, the rash develops earlier and achieves its full bloom within two or three days after its initial appearance. It is most commonly distributed in a uniform manner over the trunk and later over the extremities. The leukocyte count is almost always elevated. Final confirmation of the diagnosis rests upon the appearance of agglutinins against proteus organisms and of complement fixing antibodies against the *Rickettsiae* causing the disease.

Typhoid fever may be confused with certain other diseases if symptoms referable to particular systems are prominent. For instance, bronchitis and pneumonia among the pulmonary diseases, dysentery, acute appendicitis and tuberculous peritonitis among the abdominal, and meningococcic meningitis among the diseases of the central nervous system. Other diseases which occasionally cause difficulty are the secondary stage of syphilis, the cryptogenic form of tularemia, trichinosis, pyelitis, osteomyelitis, encephalitis, relapsing fever, meningococcemia and other bacteremias, Hodgkin's disease and lymphosarcoma. Most cases of paratyphoid fever can be differentiated from typhoid only by cultures and agglutination tests (see Salmonella Infections).

PROGNOSIS

Typhoid fever causes death in about 10 to 15 per cent of its victims. The fatality rate is higher than this in children under two years of age and in adults over thirty years. It is especially high in the aged. When certain features are present the prognosis is considerably worse. Severe toxemia is the most frequent of these, especially when accompanied by delirium or coma. Perforation is the most serious complication. Patients do not always recover from it when an operation is performed and probably never without operation. Hemorrhage, though most frequently encountered, is not often fatal.

The question of the case fatality rate in patients who have previously been vaccinated is an important one, since the number of persons who receive the vaccine is increasing all the time. Although Vaughan[19] reported a death rate of 12.4 per cent among soldiers who contracted typhoid fever in Europe during World War I, and who had previously received one or more courses of vaccine, this relatively high rate may be explainable by the presence of fatigue and of other diseases, especially dysentery. Furthermore, he included in his series only those patients from whom the organism could be cultured, thus tending to eliminate milder cases with a less serious prognosis. Malbin[9] observed a case fatality rate during an epidemic of 4 per cent among previously vaccinated patients as compared with 10 per cent among nonvaccinated individuals. Callender[3] also reported an epidemic which resulted in the death of 7 per cent of the vaccinated persons affected, as compared

with 13 per cent of the nonvaccinated persons The preponderance of evidence therefore favors the viewpoint that vaccination completely prevents most individuals from developing typhoid fever and saves the lives of many of the others even though they become ill with it

PREVENTION

The most important factor in the prophylaxis of typhoid fever is the interruption of the transit of bacteria from the feces of patients or carriers into the mouths of susceptible persons This involves the isolation of the typhoid patient and the disinfection of his excreta (see p 24) the proper disposal of sewage the purification of water supplies and the prevention of food handling by carriers

Vaccination The second factor in prophylaxis is the administration of typhoid vaccine to all persons likely to be exposed to patients with the disease or to partake of contaminated food or drink These include doctors nurses and other attendants of typhoid patients soldiers dwellers in rural areas summer campers and travellers to countries where the sanitary precautions are unsatisfactory or questionable

Exhaustive studies by Siler[17] demonstrated that the typhoid bacilli used for vaccination should be virulent strains Furthermore while a full course of three injections is the best method for the initial vaccination a satisfactory procedure for revaccination was found to be one injection of 0 5 cc subcutaneously or 0 1 cc intracutaneously Longfellow[8] confirmed the value of single doses for revaccination and stated that it should be carried out every one or two years

Vaccines which are commercially available at the present time usually contain in each cubic centimeter one billon *Eberthella typhosa* organisms and one half billion each of *Salmonella paratyphi A* and *B* organisms For an initial vaccination three subcutaneous injections of 0 5 1 and 1 cc respectively should be given at seven day intervals Satisfactory immunization is obtained if the intervals are slightly longer than seven days but they should not be shorter A person likely to be exposed to infection again should be revaccinated every year[8] For this purpose a single intracutaneous injection of 0 1 cc is preferable although a subcutaneous injection of 0 5 cc may be employed instead

After the subcutaneous injections particularly the full dose of 1 cc mild or moderately severe local reactions frequently occur General reactions such as malaise generalized aching and low grade fever appear in a small percentage of subjects

The severity of reactions to subcutaneously administered typhoid vaccine tends to increase with the number of times the individual is revaccinated[8] For this reason the intracutaneous method is superior for revaccination since it produces few reactions of any kind and rarely causes a severe reaction

TREATMENT

Typhoid fever remains one of the few bacterial diseases for which no specific therapeutic agent is available at the present time. Serums, whether obtained from convalescent patients, from immunized human donors or from animals immunized with typhoid bacilli, have never been proved to be of any value. The sulfonamides, although they are active against the *Eberthellae* in vitro, are useless in the treatment of the disease.

Streptomycin. At present the effectiveness of streptomycin is being evaluated.[5, 11] The dose used has varied, 1 gm. per day intramuscularly in divided doses having been most commonly employed. In some instances streptomycin was given orally in addition. Up to the present time we, as well as others, have seen no evidence that this antibiotic either shortens the course or modifies the complications of the disease. More patients will have to be treated before it can be determined whether it lowers the case fatality rate. Our present opinion is that streptomycin, if it is to have any effect at all, must be given early in the disease, and even then its value is doubtful.

Penicillin. Since the typhoid bacillus is relatively resistant to penicillin, no hope was entertained that this antibiotic would be useful in typhoid fever until Bigger[1] found that combinations of 10 mg. of sulfathiazole and 2 units or more of penicillin per cubic centimeter would inhibit the growth of typhoid bacilli in vitro. Although promising results have been reported[11] in six cases in which this combination was given, more patients must be studied before convincing proof of its value can be obtained.

Bacteriophage. For many years bacteriophage has been used by occasional investigators without any convincing evidence being obtained that this agent will shorten or otherwise modify the course of typhoid fever. Recently Knouf[6] reported good results following the intravenous administration of type-specific bacteriophage in fifty-six patients. The fatality rate for the series was 5 per cent. Further study of more cases is needed before this method of therapy can be properly evaluated. Our principal recourse then is to symptomatic and supportive treatment.

General Care. *Absolute rest should be insured by keeping the patient* in bed in comfortable and quiet surroundings. A nurse or a competent substitute should be in constant attendance in order to conserve the patient's strength. Sedatives and hypnotics should be given when necessary to insure proper rest.

The patient should receive daily baths, and the skin of the back should be rubbed several times a day and dusted with talcum in order to prevent pressure sores. The teeth should be cleaned and a mouth wash used after each meal. If the patient is unable to do this, the teeth and mouth should be cleansed by the nurse. Isolation precautions

involve proper disposal of all specimens of feces urine and vomitus and treatment of the linen and clothing The patient s dishes should be boiled immediately after removal from the sick room (see p 24)

DIET This is one of the most important factors in the management of the typhoid fever patient There is a considerable amount of tissue destruction during the disease which can be prevented if enough carbohydrates are given to spare the proteins Each day s diet should contain protein in the amount of 1 gm per kg of body weight The remainder should be made up mostly of carbohydrates with a small proportion of fat to a total of 60 to 80 calories per kilogram of body weight The diet consists of liquids or solids of low roughage content It is made up principally of the foods shown in Table 41

Every attempt should be made to see that the patient takes the full amount of the diet or more if he desires unless it produces un

TABLE 41

FOODS RECOMMENDED IN TYPHOID FEVER

	Basic Diet	*To Be Added if Patient s Condition Allows*
Proteins	Eggs milk cottage cheese	Scraped beef gelatin
Fats	Butter cream	Ice cream
Carbohydrates	Potatoes crackers toast boiled rice lactose	Cooked cereals (such as Cream of Wheat hominy grits and strained oatmeal) puréed vegetables fruit juices without skins or seeds custards junket tapioca jellies

Lactose is used for sweetening instead of sucrose in order to provide more calories

toward symptoms such as distention or diarrhea In the latter event the offending food should be removed from the diet or the quantity lowered Usually the patient s appetite is poor in the first two or three weeks of the disease so that he will take less than the optimal number of calories each day Later his appetite usually improves and he may eat more than the expected amount Olmstead[8] has devised a synthetic diet composed of mixtures of amino acids dextrose salts and oil emulsified in gelatin This can be given through an in dwelling stomach tube in two to four hour feedings At least 3000 cc of fluids should be given in each twenty four hour period

VITAMINS Even though a well planned diet will probably contain sufficient vitamins it is best to give supplemental vitamins to make assurance doubly sure The following amounts should be sufficient for each twenty four hour period Vitamin A 50 000 units vitamin C 200 mg vitamin D 5000 units thiamine chloride 10 mg

Symptomatic Treatment When the temperature becomes especially high a tepid sponge bath will serve to bring it down two or three degrees which should be all that is desirable The intensive tubbing of the patient in cold water which was popular in the past is no longer employed now that we realize that fever far from being harmful per se is an important factor in resistance to bacteria

Distention may be due to overfeeding in which event it can usually be relieved by diminishing the carbohydrate intake especially by omitting lactose Occasionally eggs may cause it When distention is present and the usual methods of heat and turpentine stupes to the abdomen enemas and the insertion of a rectal tube are not sufficient to relieve it pitressin may be given in doses of 0 5 to 1 0 cc ($7\frac{1}{2}$ to 15 minims) If this measure is not successful 95 per cent oxygen should be administered by inhalation

Constipation is cared for by a small enema on alternate days Mineral oil by mouth may also be needed in some cases When diarrhea occurs the diet should be investigated to see whether it might be the cause Roughage or fats in the diet may be precipitating factors If the diarrhea cannot be stopped by a change in the diet it should be treated with large doses of bismuth If these are unsuccessful opiates must be used although they should be given only as a last resort since they tend to produce distention

The patient with delirium should be watched carefully and restraints applied when necessary Sometimes this symptom can be controlled by a sponge bath to bring the temperature down If necessary bromides paraldehyde barbiturates or opiates should be administered

Treatment of Contacts The physician should instruct all persons who come in contact with the typhoid patient how to avoid infecting themselves In spite of repeated warnings however a fairly high percentage of these persons develop the disease Accordingly it is best to immunize household contacts as soon as the diagnosis is made Doctors and nurses should of course always be vaccinated The necessary procedures have been outlined on page 268 Ramsey[14] found that whereas about 7 per cent of nonimmunized contacts contracted typhoid only about one-fourth as many immunized contacts developed the disease

Treatment of Complications INTESTINAL HEMORRHAGE A few clots of blood in the stool do not call for any special treatment except careful observation of the patient in order to detect the first evidence of a large hemorrhage should it occur As soon as a sizeable hemorrhage is detected the patient should be put at rest All distractions should be kept out of the sick room and sedatives given when needed Since opiates tend to produce distention these should not be used unless proper rest cannot be obtained with other drugs Feeding by mouth should be stopped and only enough water given orally to allay thirst

Food and fluids should be given subcutaneously or slowly by vein. In our opinion there are no drugs which will have the slightest effect upon bleeding The patient s blood type should be determined im mediately but transfusions are best held in reserve until there is a fall in the hemoglobin below 50 or 60 per cent and they should be given slowly It is best to let the bowels rest for three or four days after a hemorrhage before food and enemas are given again

INTESTINAL PERFORATION This requires immediate operation so that the perforated area may be closed There is no question as to treat ment The difficulty usually lies in the diagnosis A surgeon should be called in consultation whenever there are suspicious symptoms of perforation If an operation is decided upon it should be started and completed as quickly as possible Even under the most favorable cir cumstances recovery does not always follow operation Stuart[18] reported that among eight patients who underwent surgical intervention only three survived

PHLEBOTHROMBOSIS The affected extremity should be elevated on a pillow kept at rest and heat applied in the form of an electric pad or hot water bottle Because of the possibility of an embolus to the lungs it is best to ligate the vein above the thrombus

PNEUMONIA If this is caused by the pneumococcus or is a mixed infection it may be treated with penicillin or sulfonamides as indi cated in the section on pneumococcic pneumonia (see page 117) If it is due to the typhoid bacillus these agents will be of no value

CHOLECYSTITIS This usually subsides with symptomatic treatment but if perforation of the gallbladder seems imminent cholecystectomy must be done A surgical consultant should be called when the first evidences of this complication appear Since an operation is extremely hazardous for a patient with typhoid it is fortunate that it is seldom necessary

Treatment of the Carrier State About 3 per cent of typhoid patients continue to have *Eberthellae* in their stools or urine for a year or more after recovery from the disease Saphir[16] found that among 110 chronic carriers sixty five were bile carriers forty three were intestinal carriers (organisms being present in the stools but not in the bile) and two were urine carriers Formerly the only treatment for bile carriers was removal of the gallbladder Coller[4] was successful in eradicating bacteria from sixteen of eighteen carriers on whom he performed this operation Since it is difficult to persuade a person who is feeling perfectly well to undergo this ordeal there has been an intensive search for drugs which would rid the gallbladder of in fection A fair degree of success has been achieved by the use of tetra iodophenolphthalein in doses of 4 gm (60 grains) three times a week until a total of forty doses are given. The sulfonamides especially the poorly absorbable ones such as succinylsulfathiazole may also

be successful in eradicating the carrier state in some cases Much more work remains to be done before their value can be assessed This is also true of streptomycin administered orally

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Salmonella typhimurium was the commonest strain followed by *S newport* and *S choleraesuis* *Salmonella paratyphi* A causes many more infections than are indicated from this study The reason so few are listed here is undoubtedly that the latter organisms are usually identified in the laboratories in which they are originally cultured and need not be sent on to a salmonella center for identification

In contrast to the single clinical picture which results from infection with *Eberthellae* namely typhoid fever the salmonella organisms cause different types of infections They are classified as (1) gastroenteritis (2) salmonella fever which is essentially a typhoidal type of bacteremia and (3) various localized infections To this might be added a fourth group in which the *Salmonellae* are secondary invaders in the presence of infections caused by unrelated bacteria or during the course of other diseases The clinical picture of bacteremia and fever caused by S *paratyphi* A B or C has in the past been called paratyphoid fever Now that we realize that the paratyphoid organisms represent a small part of the large group of *Salmonellae* all of which produce the same clinical picture the term paratyphoid fever should be discarded in favor of the more inclusive term salmonella fever

It will be noted from Table 12 that most strains produced gastroenteritis more frequently than any other clinical syndrome with the exception of *S paratyphi* A and B and *S choleraesuis* which more often caused salmonella fever Each of the organisms however with the exception of S *paratyphi* A was in some instances responsible for any one of the three types of diseases

Salmonella infections occur in all age groups Approximately three-fifths occur in adults and about one-fifth each in children and infants

Salmonella Fever

About one-sixth of all salmonella infections produce a syndrome which varies in severity from a high continued fever similar to that found in typhoid fever with considerable toxicity and a grave prognosis to a short low grade fever of one or two weeks duration accompanied by nothing more than mild malaise Anorexia vomiting and abdominal distention are present in most patients Abdominal pain and diarrhea are frequently seen Other systems may be affected as follows respiratory system coryza cough and physical signs of bronchitis nervous system headache nearly always also drowsiness convulsions and delirium musculoskeletal system general aching pain in the back and arthralgia In general the illness differs from typhoid fever by a more abrupt onset a shorter period of time before the fever reaches the plateau stage and a more abrupt termination In salmonella fever the symptoms are generally milder and gastrointestinal symptoms more common Rose spots enlargement of the spleen relative bradycardia hemorrhage and perforation are less frequent

14 Salmonella Infections

(Salmonella Fever, Salmonella Enteritis, Paratyphoid Fever)

Salmonella is a genus of gram negative bacteria which differs in fermentation reactions from the other members of the coli aerogenes group and slightly from *Eberthella typhosa* In addition to common cultural characteristics the salmonella organisms have certain antigenic relationships and are all pathogenic for man or animals They are more important than the physician usually considers them since

TABLE 42

Salmonellae WHICH FREQUENTLY CAUSE HUMAN INFECTIONS AND THEIR CLINICAL MANIFESTATIONS†

Group	*Salmonella*	*No of Infections*	*Deaths*		*Principal Clinical Features*		
			Number	*Per cent*	*Gastro-enteritis*	*Bacteremia*	*Local Infections*
A	Paratyphi A	8	0	0	0	8	0
B	Paratyphi B	101	2	2	31	63	7
	Typhimurium	602	41	7	548	22	32
	Derby	39	2	5	28	10	1
C_1	Cholerasuis	127	30	24	29	63	35
	Oranienburg	102	7	7	82	9	11
	Montevideo	70	2	3	61	5	4
C_2	Newport	180	8	4	159	9	12
D	Enteritidis	36	3	3	26	3	7
	Panama	71	2	3	52	13	6
E	Anatum	52	1	2	46	3	3

Since the individual strains in Group F are seldom encountered none of these are included in the table

† Data taken from the studies of 3000 cases reported by Seligmann[24]

* The principal clinical feature most frequently caused by each strain is shown in bold face type

they are responsible for a number of different kinds of infections and at the present time cause many more illnesses than the typhoid bacillus

Each strain is classified into one of the groups from A to F according to its somatic antigens and as an individual strain according to its flagellar antigens The strains of *Salmonellae* of most importance in human infections and the frequency with which they were encountered by Seligmann[3] at his Salmonella Center are shown in Table 42

diagnosis is to culture the salmonella organisms from the blood stream bone marrow stools or urine (in cases of salmonella fever) from the stools (in cases of enteritis) and (in patients with localized infections) from the area involved or from the blood stream

In nearly every instance the organism can be identified as belonging to the salmonella group by its cultural characteristics Identification of the specific type on the other hand is not easy If the local laboratory is not equipped to study the strain in this way the organisms should be sent to one of the salmonella centers such as those at the University of Kentucky Lexington Kentucky and at the Beth Israel Hospital New York City

The agglutination test using the patient s serum yields similar information and involves the same uncertainties as the agglutination test in typhoid fever Agglutinins as a rule are not present until the second or third week of the disease and occasionally not at all They may indicate a previous infection with salmonella organisms or they may be due to infection with some other agent The test is not always positive when run against the organism causing the disease therefore analytical agglutination tests should be run against the O antigen and against the two separate H antigens If the etiologic organism is unknown the proper procedure is to run agglutination tests against certain combinations of salmonella antigens

The leukocytes behave in an interesting manner in the different salmonella infections In salmonella fever as in typhoid fever the leukocyte count is rarely above 10 000 per cu mm and is often below 5000 In the localized infections leukocytosis is the rule The white blood cell count may go as high as 20 000 per cu mm or more as in pyogenic infections with other bacteria In gastroenteritis the leukocyte count usually falls between the two extremes observed in the clinical syndromes mentioned above In cases of mild gastroenteritis there is no elevation of the leukocyte count If the disease is more pronounced there will be a slight or occasionally a moderate leukocytosis In the differential count the proportion of lymphocytes is relatively increased especially in the salmonella fever cases

Diagnosis Salmonella fever should be suspected in patients with continued or irregular fever especially if the temperature climbs to its plateau stage faster than is usually the case in typhoid fever Any of the symptoms or signs which are often encountered in typhoid fever such as diarrhea constipation distention cough and signs of bronchitis rose spots or enlarged spleen may be present in salmonella fever The only certain method of distinguishing the disease from typhoid fever is by laboratory tests Culturing the organisms from the blood bone marrow stools or urine is more reliable than obtaining a high agglutinin titer against salmonella antigens If cultures fail however a rising titer of salmonella agglutinins plus the clinical mani

Complications may occur as the result of localization of the bacteria in various parts of the body These are similar to the local infections which take place without accompanying salmonella fever and will be discussed under that heading

Salmonella Gastroenteritis

This is the clinical picture produced by about 75 per cent of the salmonella infections The incubation period varies from four to seventy two hours after the contaminated food is eaten The onset is sudden with vomiting followed by diarrhea or with diarrhea alone The stools may be merely liquefied feces or may contain blood and mucus Severely ill patients may have high fever abdominal cramps tenesmus prostration and general malaise Cramps in the leg muscles and muscular twitchings are other symptoms of severe attacks Chilly sensations are experienced by most patients and actual chills are occasionally present

Such violently ill patients are not the rule however Most patients have diarrhea temperature of 102 F or less and slight malaise In a few the only evidences of the salmonella infection will be a few loose stools without fever or other symptoms In mild cases the entire illness will be over in less than twenty four hours even in the severest cases it seldom lasts more than a week Except in the milder cases the patient feels weak and listless for a day to a week after the active stage of the disease has gone Chronic gastroenteritis with diarrhea and abdominal discomfort caused by salmonella organisms has been reported Complications similar to those seen in salmonella fever occasionally occur but are much less common

Local Salmonella Infections

Salmonellae cause local infections in practically any part of the body About one sixth of the salmonella infections are of this type In the abdominal cavity they may cause appendicitis cholecystitis or peritonitis Rubenstein[1] has reported eighteen patients with salmonella infections who were operated on because they showed the clinical picture of appendicitis Only seven of them were found actually to have appendicitis although all had typical symptoms The physician s dilemma is made more serious by the fact that an appendix acutely infected with *Salmonellae* will sometimes rupture In the respiratory tract bronchitis bronchopneumonia lobar pneumonia pleural effusion or empyema may be observed Among these infections pneumonia is especially frequent and is often found in association with local infections elsewhere in the body Osteomyelitis and pyarthrosis are fairly common Other local infections are purulent meningitis pyelonephritis salpingitis endocarditis and abscesses in various parts of the body

Laboratory Examinations The only sure method of making the

Salmonella enteritis likewise must be treated symptomatically. Severe diarrhea should be checked by 4 cc (1 dram) of paregoric or 0.6 cc (10 minims) of tincture of opium or proportionate doses in children. Patients who are vomiting may be given opium suppositories or *morphine by injection*. Bismuth salts and kaolin may be used in milder diarrheas and in conjunction with the opiates in the severer ones. The patient should be encouraged to take large quantities of fluid by mouth, but if it is obvious that more fluid is being lost than is being taken in, isotonic saline solution should be given subcutaneously or intravenously. Dextrose may be added to the latter if the patient has gone for some time without food. When the patient is able to eat he should be given a bland high caloric diet and within two days to two weeks after all the symptoms have disappeared may be placed *on a full diet again*.

SULFONAMIDE TREATMENT. Certain strains of *Salmonellae* are sensitive to the sulfonamides, although the majority are not. It is worth while, therefore, to try sulfonamides in severe enteritis and in local infections with *Salmonellae*, *although they may not always be beneficial*.

In salmonella pneumonia and meningitis, sulfadiazine or sulfamerazine should be given systemically in full doses.

STREPTOMYCIN TREATMENT. Combined oral and intramuscular therapy with streptomycin has apparently succeeded in eradicating salmonella enteritis. Doses of 100 mg per kilogram of body weight per day may be given orally to infants and 4 gm a day to adults. For intramuscular administration 1 to 3 gm may be tried. Streptomycin should also be tried in cases of meningitis in doses of 2 to 6 gm a day intramuscularly and 25 to 50 mg intrathecally daily.

TREATMENT OF LOCAL INFECTIONS. Local infections should be treated surgically wherever they are accessible and operation is indicated.

ISOLATION PRECAUTIONS. Patients with salmonella fever or enteritis should be isolated and their excreta disinfected as in typhoid fever. Patients with localized salmonella infections should likewise be isolated. Typhoid vaccine as it is available commercially contains *Salmonellae paratyphi* A and B as well as *Eberthellae* so that it can be used to protect attendants of patients ill with these infections.

References

1 Rubenstein, A. D., and Johnson, B. B.: Salmonella Appendicitis, Am. J. M. Sc. 210:51, 194

2 Seligmann, E., Saphra, I., and Wassermann, M.: Salmonella Infections in Man. An Analysis of 1,000 Cases Bacteriologically Identified by the New York Salmonella Center, Am. J. Hyg. 38:226, 1943.

3 Seligmann, E., Saphra, I., and Wassermann, M.: Salmonella Infections in the U.S.A. A Second Series of 2,000 Human Infections Recorded by the New York Salmonella Center, J. Immunol. 54:69, 1946.

General Article

Bornstein, S.: The State of the Salmonella Problem, J. Immunol. 46:439, 1943.

festations of salmonella fever constitute fairly reliable criteria Any diarrhea of a few hours to a few days duration accompanied by varying degrees of fever and constitutional symptoms may indicate a salmonella enteritis The diagnosis must be made by finding the organisms in the stools although a presumptive diagnosis may be made in an epidemic by finding them in food eaten by all the victims There is nothing distinctive about the local infections caused by the organisms The laboratory must again be relied upon to make the diagnosis

DIFFERENTIAL DIAGNOSIS For salmonella fever the differential diagnosis is the same as that for typhoid fever From typhoid fever itself there can be no certain differentiation without the aid of the laboratory although salmonella fever tends to be shorter and milder and to have fewer serious complications than typhoid fever

Salmonella enteritis usually has a longer incubation period than staphylococcic intoxication On the other hand all the characteristics of the salmonella infections are present in shigella dysentery and the differentiation here must be made entirely on laboratory grounds For a further differential diagnosis for diarrheas see Shigella Infections Table 43 page 286

Prognosis Salmonella fever is more benign than typhoid fever as would be expected from its short course and lower incidence of serious complications The case fatality rate is about 1 to 5 per cent Patients with salmonella gastroenteritis almost invariably recover Infants or aged patients may succumb if their infection is serious

The prognosis in the local infections depends upon the organ or area involved and its accessibility to surgical treatment and upon the age and general condition of the patient The fatality rate is definitely higher for local infections in general than it is for salmonella fever or gastroenteritis

Prevention Salmonella infections are prevented by the same measures employed against eberthella infections Sanitary precautions are even harder to carry out in salmonella infections however since animals carry many of the strains and human carriers are more numerous and harder to detect

Vaccination can be employed against *Salmonella paratyphi A* and *B* organisms since these are contained in the standard typhoid paratyphoid vaccines which are commercially available The procedure consists in three subcutaneous injections of 0 5 1 0 and 1 0 cc respectively seven or more days apart Details of vaccination and revaccination are given on page 268

Treatment The treatment of salmonella fever and its complications is the same as for typhoid fever The sulfonamides and penicillin do not have any demonstrable effect upon either disease The value of *streptomycin* is questionable (See the chapter on Typhoid Fever for more details)

deep as the muscularis. Perforation occurs rarely. *Shigella dysenteriae* secretes exotoxins which are absorbed into the body and are responsible for the extreme severity of this form of the disease but as far as can be determined the other *Shigellae* produce only an endotoxin.

SYMPTOMS AND SIGNS

The incubation period while it may extend over a week or more is usually short from one to four days. In an occasional patient the illness may begin as early as twelve hours after the ingestion of the contaminated food or drink. The symptoms may be classified as focal (related to the intestines) and general. The earliest symptom is most often abdominal pain followed in a short time by diarrhea. Some patients on the other hand experience general symptoms first.

Local symptoms are diarrhea abdominal pain vomiting tenesmus and rectal burning. In 37 per cent of our patients with Flexner and Sonne infections there were three stools a day or less in 13 per cent there were four to nineteen stools within a twenty four hour period while 20 per cent of the patients had over twenty stools a day. The stools at first retain their fecal character but the amount of mucus and blood gradually increases until in the severer cases the patient is passing only watery mucus pus and blood. Among our patients 8 per cent passed what appeared to be pure blood at some time during the disease and an additional 22 per cent had stools which were streaked with blood.

The characteristic abdominal pain is griping in nature and is relieved by defecation. It is most often in the region of the umbilicus but may involve any part of the abdomen. Seventy six per cent of our patients who were over two years of age complained of it. Some degree of tenesmus is present in all but the milder cases. Rectal burning and soreness is a characteristic complaint. Vomiting may be incessant or may be limited to the onset.

General symptoms are fever chills or chilly sensations malaise general aching and convulsions. Fever is an extremely variable symptom. Ten per cent of our patients had none at all at least not after they arrived in the hospital. In 59 per cent the temperature was elevated one to three degrees while 31 per cent of the patients had temperatures which reached 104° to 106 F. Frank chills were present in 15 per cent and chilly sensations in 17 per cent of the patients over two years of age. Because many of our patients were children our data regarding chilly sensations malaise and general aching are inadequate. These are common complaints in adults. Meningismus was present in 6 per cent of patients and convulsions in 9 per cent. These complications are almost always confined to children.

Examination of the abdomen usually reveals generalized tenderness and at times rigidity. Sometimes a spastic colon or terminal ileum

15 *Shigella Infections (Bacillary Dysentery)*

The *Shigellae* are gram negative bacilli which are differentiated as a group because they have certain distinct cultural characteristics and because the majority of them produce diarrhea in humans The disease they cause is an acute or chronic inflammation of the colon and sometimes also of the distal ileum and is commonly called bacillary dysentery *Shigellae* comprise four main groups *Shigella dysenteriae* (the Shiga bacillus) *Shigella ambigua* (the Schmitz bacillus) *Shigella paradysenteriae* (including mostly the various types of the Flexner bacillus and several additional strains designated as Boyd types) and *Shigella sonnei* (the Sonne Duval bacillus) *Shigella paradysenteriae* and *Shigella sonnei* are the types most frequently encountered in patients and carriers in the United States and in temperate climates in general In tropical countries any of these four types of *Shigellae* may be found

Bacillary dysentery is spread when the organisms are transmitted from human feces to the mouths of other individuals Whatever shortens that pathway or facilitates transmission along it increases the incidence of the disease The disease will spread for instance when the usual rigid sanitary precautions of civilized society are relaxed whether owing to crowding as in schools barracks and prisons to lack of intelligence as in institutions for the insane to poverty to war or to a desire to get back to nature as in summer camps The frequency of the disease is not decreasing along with the lessening of the incidence of typhoid fever This may well be due to the prevalence of unrecognized carriers in the general population Watt[4] for instance in a recent study conducted in Puerto Rico New Mexico Georgia and New York City found an average of 9 1 carriers for each current case of dysentery Epidemics have been traced to contaminated water ice milk and various foods Flies frequently carry the organisms and perhaps ants also

As might be implied from the way it is spread bacillary dysentery is more often encountered during the warmer months of the year and in warmer climates While it occurs most commonly in children from one to ten years of age it affects persons of all ages

When shigella organisms are ingested they may be killed in the stomach if the acidity is high If they survive to infect the intestine they cause inflammation of the mucosa of the colon and sometimes of the terminal portion of the ileum with diffuse hyperemia at first This is followed by the formation of a diphtheritic membrane and ulceration which may involve only the mucosa or may extend as

centage of patients with positive cultures was much higher when the following procedure is employed. The wrapped portion of a cotton applicator is placed in a glass tube, the end of which has previously been rounded off by heating in a flame. The applicator and the glass tube are sterilized, and when they are to be used the glass tube is lubricated (without covering the open end) and inserted into the rectum. The applicator is then pushed forward and swept around the rectal mucosa with a circular motion, pulled back into the tube, and the tube withdrawn. The applicator is streaked directly across a Shigella-Salmonella agar plate. This is a modification of the procedure used by Hardy,[4] who employs a rubber instead of a glass tube.

When it is possible to do so, cultures should be taken through the sigmoidoscope. Felsen[1] has devised a long capillary tube equipped with a rubber bulb for aspirating material from the intestinal crypts. The contents of the tube may be sprayed immediately upon the surface of the plate containing the differential medium.

Agglutination tests for dysentery bacilli have never achieved the popularity of agglutination tests for typhoid and salmonella infections, and deservedly so. For one thing, bacillary dysentery is usually a short-lived disease. The diagnosis is certain in most patients, and by the seventh to the tenth day, when agglutinins appear, they are well on the way to recovery. This test is therefore more valuable in the diagnosis of the chronic form of bacillary dysentery. Another drawback to the test is that many persons without dysentery exhibit a significantly high titer of agglutinins. In spite of these limitations the test may supply useful information on an occasional patient with a protracted bout of dysentery for which the cause has not been determined with certainty. It should be repeated at intervals of three to five days because a rise or fall in the titer will often be significant, and because the titer may be elevated for only a few days in all.

Blood cultures should be taken, although they are of less value than in most infectious diseases, since the organisms are rarely found in the blood. None of our patients had positive blood cultures.

COMPLICATIONS

Local complications are infrequent. Perforation is rare, much more so than in typhoid, for instance. Intussusception occurs occasionally in children. Prolapse of the rectum is seen a little more often. Appendicitis due to Shigella organisms is likewise rare. Abscesses in nearby structures such as the rectus muscles and the ischiorectal fossa have been reported. Stenosis of the bowel as a result of the formation of scar tissue during healing is an infrequent occurrence.

General Complications. Among the general or systemic complications, arthritis is perhaps the most frequent. It makes its appearance during the second or third week of the disease in most instances and

can be felt The spleen was palpable in 1 5 per cent of our patients while Smith[6] detected the spleen in 8 per cent of eighty seven adults with Shiga dysentery

Course When specific treatment is not given the local and general symptoms will subside spontaneously usually within from three to ten days infrequently within a shorter or longer period of time

Clinical Types Slight general symptoms may be present along with slight or with severe local symptoms and likewise severe general symptoms may be combined with local symptoms of any severity On the one extreme are the very mild cases where there is little or no malaise and only a few (one to five) semi liquid or liquid stools a day for a day or two On the opposite extreme are the patients who have chills vomiting and the rapid onset of severe watery diarrhea followed by prostration and collapse

Laboratory and Special Examinations

The *leukocyte count* was above 10 000 per cu mm in 28 per cent of our patients the extremes being 5000 to 15 000 The polymorphonuclears were over 75 per cent in 53 per cent of the patients and there was a shift to the left in 35 per cent of the patients Of more significance is the fact that at least one of these abnormalities was present in three fourths of all the patients

Proctoscopic examination is helpful in diagnosis According to Smith[6] in the early stage the disease is characterized by diffuse hyperemia and edema of the mucosa which is dotted with hemorrhages and pin point to pinhead size miliary abscesses In the more acute cases there may be diffuse superficial necrosis of the mucosa followed by the formation of a pseudomembrane In the middle phase granulations are seen at the sites of previous necroses or abscesses Ulcers 0 5 to 1 mm in diameter may be present in the center of the granulations A late ulcerative phase may occur after acute dysentery in patients who have not received sulfonamides These ulcers have a dirty grayish base with little or no reaction around the edges and leave superficial scars when they heal

Microscopic examination of the stools is of some diagnostic importance The stools are loaded with leukocytes the majority of which are poly morphonuclears After the first day or two numerous red blood cells are also present

Culture of Feces If stools are to be relied upon for identification of the etiologic agent they should be sent to the laboratory promptly A portion is then plated upon Shigella Salmonella agar Endo agar or one of the other media which will differentiate the dysentery and other pathogenic organisms from *Escherichia coli*

A much better method than stool culture is the use of the rectal swab At Gallinger Municipal Hospital we have found that the per

times in the terminal ileum Proctoscopic and roentgenologic examinations are essential to the diagnosis *Shigellae* are not obtained upon culture so frequently as in the acute cases Some authors notably Felsen[1] believe that the majority of cases of chronic ulcerative colitis are the sequels of an infection by the dysentery bacilli

Adult patients who have the underlying psychosomatic mechanism conducive to spasticity of the colon may develop a spastic colon after a severe bout of bacillary dysentery We have seen several such cases in patients who had shigella dysentery while traveling abroad under conditions of stress in wartime Roentgenograms of the intestines and cultures of the stools will be needed to rule out chronic bacillary dysentery in persistent cases

Diagnosis

When abdominal cramps and diarrhea appear suddenly in an otherwise well individual a shigella infection is always a strong possibility The diagnosis of bacillary dysentery can be made with certainty only by obtaining the organisms on culture from the rectosigmoid or from the stools or by observing the characteristic appearance of the mucosa through the sigmoidoscope

Differential Diagnosis Other diseases which commonly cause diarrhea are shown in Table 13 It is evident that staphylococcic intoxication can be separated out from all the others by the brevity of its incubation period and indeed of its entire course Likewise the clinical features are usually sufficient to differentiate typhoid and salmonella fevers and amebic dysentery from shigella infections Salmonella gastroenteritis on the other hand can practically never be distinguished from bacillary dysentery on the basis of the clinical picture A diagnosis must be made either by isolating the causative organism or by sigmoidoscopic examination or both

Certain features in addition to those given in the table are helpful in distinguishing amebic from bacillary dysentery The stools in the former are usually copious in quantity fecal in character and mixed with blood and mucus while in the bacillary type they tend to be small in amount homogeneous gelatinous and mixed with bright red blood Microscopically the former contain a scant quantity of cells most of which are mononuclear in contrast to the stools in shigella dysentery which are characterized by an abundance of cellular exudate in which the polymorphonuclears predominate over the monocytes Furthermore in bacillary dysentery all the cells appear much more badly damaged When the material aspirated from the amebic ulcers is examined under the microscope the motile trophozoites are usually seen The stools may contain these forms or the cysts Typical amebic ulcers as seen on sigmoidoscopic examination are usually single although occasionally two of them coalesce Their edges are undermined

involves the larger joints especially In this respect and because it is characterized by involvement of the periarticular tissues and the tendon sheaths it closely resembles gonococcic arthritis The joints may contain serous fluid and are usually sterile If the joints are acutely inflamed the local manifestations will be accompanied by an exacerbation of fever The arthritis subsides within one to three weeks in most patients although an occasional patient may be afflicted with it for several weeks or months

Ocular complications occasionally observed are conjunctivitis iritis and iridocyclitis They appear at about the same time that arthritis is to be expected

Respiratory symptoms characteristic of coryza bronchitis pleurisy or pneumonia are noted fairly frequently in children with the disease Otitis media is also a complication in children Most of these infections are probably due not to dysentery bacilli but to other organisms which take advantage of the debilitated state of the patient

Complications which result from the diarrhea and vomiting especially if these symptoms are prolonged are dehydration tetany avitaminoses (especially those due to lack of the B complex) edema and ascites The last three are seen particularly in patients whose diet was inadequate before the onset of the infection

Other complications rarely seen are meningitis myelitis encephalitis brain abscess endocarditis urethritis and vaginitis

Pyelitis and pyelonephritis sometimes result from infection with shigella organisms but they are not usually found in conjunction with dysentery

RELAPSING AND CHRONIC DYSENTERY In view of the multiplicity of types of dysentery bacilli and the common failure to make careful bacteriologic studies at the outset it is often difficult to judge whether a second episode of diarrhea is really a relapse or a new infection with another strain Simple recurrence of diarrhea may often be brought about by taking a cathartic a day or two after the frequent stools have stopped In other patients immunity may not be complete so that the disease may appear again for a short period of time In others the inflammation and ulceration of the bowel remains and the disease enters a chronic stage

Chronic bacillary dysentery runs a course measured in years rather than in months Long periods in which there is no diarrhea at all or there are only a few semisolid stools each day are interspersed with episodes of fever malaise abdominal cramps and watery stools which contain mucus and often blood After the disease has persisted for some time loss of weight vitamin deficiency and chronic ill health are almost inevitable accompaniments Some patients eventually recover while others succumb to the disease after weary years of invalidism Inflammatory and ulcerative changes are present in the colon and some

Other intra-abdominal conditions which must be differentiated are appendicitis, allergic gastroenteritis, tuberculosis, ulcerative colitis of unknown etiology, carcinoma of the intestines, mercury poisoning, and infestations with parasites.

General diseases which may be confused with dysentery, especially in children, are influenza, pneumonia and meningitis.

Prognosis

Since many cases are unreported and probably still more are unrecognized, the true recovery rate is unknown. The average case fatality rate for hospital patients before the days of the sulfonamides was in the neighborhood of 5 per cent. The death rate in epidemics has varied from zero all the way up to 50 per cent, depending upon the type of infecting organism (the Shiga strain usually causes the severest cases), the age of the patient (patients in the older age groups and particularly young children have the worst prognosis), and the patient's previous physical condition (malnutrition, exhaustion and similar factors often stand in the way of recovery).

Prevention

Bacillary dysentery can be prevented only by breaking the pathway from feces to mouth. Isolation of the patient and proper disposal of his stools are necessary on the one hand. On the other hand people must protect themselves or be protected from drinking contaminated water and eating food which has been exposed to flies or has been handled by carriers of dysentery bacilli.

Treatment

Isolation. The patient with suspected bacillary dysentery should be isolated and his stools treated so as to render them noninfectious (see p 24). Rectal or stool cultures should be obtained whenever feasible and the patient kept in isolation until the pathogenic organisms can no longer be cultured from them.

Catharsis. For centuries the argument has raged between the advocates of preliminary catharsis and those who believe it is not only unnecessary but may even be dangerous. The former claim that the bacterial toxins are retained in the gut if the bowel is put at rest without preliminary purging. Their opponents argue that the diarrhea which occurred before the start of treatment is sufficient to rid the bowel of most of the toxins and that augmentation of the diarrhea by the use of cathartics may produce more injury to the already damaged walls of the intestines.

It seems to us that the universal employment of sulfonamides in bacillary dysentery should dispose of this question. Since these chemotherapeutic agents bring about a rapid diminution in the number of

and they are surrounded by a hemorrhagic ring beyond which normal mucosa extends to the next ulcer The floor of the ulcer is composed

TABLE 43

DIFFERENTIAL FEATURES OF THE COMMON DIARRHEAS DUE TO INFECTIOUS AGENTS

Disease	*Cause*	*Incubation Period*	*Characteristic Clinical Features*	*Usual Duration*	*Laboratory Diagnosis*
Staphylococcic food poisoning	Enterotoxin produced by staphylococci	1 to 6 hours	Sudden onset of nausea vomiting and diarrhea Most persons who have eaten the same food are affected concomitantly	1 to 2 days	Culture of stools Culture of suspected food
Salmonella gastroenteritis	*Salmonellae*	4 to 72 hours	In some patients slight or moderate diarrhea with or without low fever	12 hours to 7 days	Culture from rectum Culture of stools
Bacillary dysentery	*Shigellae*	12 hours to 7 days or more	In others vomiting abdominal pain frequent stools containing blood and mucus	3 to 10 days	Culture from sigmoid or rectum Culture of stools
Typhoid and salmonella fevers	*Eberthella typhosa* *Salmonellae paratyphi A* Occasionally other *Salmonellae*	3 days to 3 weeks or more	Onset usually gradual Fever toxicity distention and symptoms referable to other systems are outstanding rather than the diarrhea	2 to 6 weeks	Culture of blood Culture of stools Agglutination test
Amebic dysentery	*Endameba histolytica*	2 to 12 weeks or more Often indeterminate	Abdominal cramps and diarrhea General symptoms are usually minimal	Months or years	Microscopic examination of stools Culture of stools

of necrotic tissue These can be compared with ulcers of bacillary dysentery described on page 282

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of necrotic tissue *These* can be compared with ulcers of bacillary dysentery described on page 282

absorption and fairly high toxicity Sulfathiazole is more effective than sulfapyridine but not so good as sulfadiazine and other absorbable compounds

Sulfadiazine has been found to be the drug of choice by Hardy[2, 3] From his two excellent studies comparing the rapidity of disappearance of the etiologic organism from the stools in patients treated with sulfathiazole sulfadiazine sulfapyrazine sulfamerazine and sulfamethazine among the absorbable compounds and sulfaguanidine succinylsulfathiazole and phthalylsulfathiazole among the poorly absorbable compounds it is evident that sulfadiazine was definitely superior to sulfathiazole and slightly superior to sulfamerazine sulfapyrazine and sulfamethazine while succinylsulfathiazole was superior to phthalylsulfathiazole and sulfaguanidine The best of the readily absorbed sulfonamides (sulfadiazine) was more effective than the best poorly absorbed compound (succinylsulfathiazole) especially in early cases After the third day and in carriers the best drug was *succinylsulfathiazole*

The superiority of the absorbable compounds is probably due to the fact that the dysentery bacilli are lodged not only in the mucous membranes but also in the deeper tissues of the intestinal walls as well as in the regional lymph nodes Compounds which attain relatively high levels in the blood would reach the organisms in these hidden places

EFFECTS OF SULFONAMIDE THERAPY When sulfadiazine is given to patients with dysentery caused by Flexner strains the number of pathogenic organisms in the feces begins to fall within twenty four hours in most instances *Shigellae* fail to grow out in rectal cultures in over half the patients within forty-eight hours and have disappeared in nearly every patient by the fourth day The temperature usually drops to 100 F or less within the first forty-eight hours and the diarrhea disappears within the same period of time

RESPONSE OF THE DIFFERENT STRAINS OF *SHIGELLAE* TO SULFONAMIDES Schmitz strains respond almost as promptly to proper sulfonamide therapy as Flexner strains Infections with *Shigella sonnei* are somewhat more resistant *Shigella dysenteriae* (Shiga bacillus) infections have not been tested on a comparative basis but according to Smith[4] their response to sulfadiazine is striking while in vitro studies show that they are about as sensitive as Schmitz strains

RECOMMENDED PROCEDURE FOR SULFONAMIDE ADMINISTRATION When the tentative diagnosis of bacillary dysentery has been made on the basis of the clinical picture a rectal swab should be taken and immediately after this the patient should be started on sulfadiazine therapy For an adult an initial dose of 4 gm (60 grains) is satisfactory followed by 1 gm (15 grains) at six hour intervals until the diarrhea has subsided the temperature has fallen and evidences of toxicity have

shigella organisms in the stools, toxin production is practically stopped within a few hours after sulfonamide treatment is initiated It is possible that in the rare patient who is constipated and at the same time very toxic catharsis may be beneficial all others appear to suffer less and to recover just as well when the bowel is put at rest at the start of *treatment*

Rest for the Bowels Tincture of opium 0 6 cc (10 minims) or camphorated tincture of opium (paregoric) 4 cc (1 dram) should be given immediately to adults and comparable doses according to weight to children This dose should be repeated every four hours until the diarrhea has stopped In our experience patients who are nauseated are able to retain the camphorated tincture better than the simple tincture of opium If they cannot do so morphine may be given subcutaneously in the usual doses

The diarrhea is likely to be followed by a period of constipation lasting usually from two to four days The patient should be cautioned not to become concerned over this since it is a natural sequel of the diarrhea accentuated by the use of opium It will end of its own accord in due time Resort to a cathartic even a mild one during this period will often start the diarrhea all over again

Sulfonamides *It is not too much to say that the treatment of* bacillary dysentery has been revolutionized by the use of the sulfonamides They have brought about a shortening of the course of the disease with more rapid fall in temperature and pulse rate speedier relief from abdominal pain and tenesmus and faster reduction in the number of stools together with the disappearance of blood from the feces

ABSORBABLE AND POORLY ABSORBABLE SULFONAMIDES The sulfonamide compounds which are only slightly absorbed from the intestine (see p 41) have certain advantages in the treatment of bacillary dysentery Since only small amounts enter the blood stream the concentration of the drug in the urine is low and renal calculi are rare For the same reason dermatitis and drug fever are less frequently observed than with the rapidly absorbable drugs Disadvantages in the use of these drugs are (1) they are expensive since the dose is *about five times as much* as with the absorbable compounds and (2) the large amount of the drug which is administered sometimes causes nausea and vomiting or diarrhea Their clinical efficacy will be discussed under the individual drugs

Practically all the sulfonamides have been used at one time or another in the treatment of shigella infections Sulfanilamide was used at first but has been discarded in favor of other compounds which are much more effective Sulfapyridine has been employed extensively It is more effective than sulfanilamide *but not so effective as sulfathiazole* and sulfadiazine and has in addition the disadvantages of irregular

Streptomycin. Where the sulfonamides are not successful in eradicating the disease, streptomycin can be tried. Pulaski[6] has had excellent results with 1 to 4 gm a day administered either orally or intramuscularly. Until more cases have been studied it is perhaps best to give 3 gm orally and 1 to 3 gm intramuscularly per day.

Bacteriophage. This substance, the value of which was controversial in the past, would seem to be needless now that the sulfonamides are employed.

Administration of Fluids. The fluid balance has always been of crucial importance in patients with dysentery because of the inevitable dehydration which follows vomiting and diarrhea. Today it is of still more significance because of the possibility that renal calculi may be formed by the absorbable sulfonamides if urinary excretion is too scanty. Even the poorly absorbable compounds may in occasional cases enter the blood stream in large amounts and form calculi in the urinary tract. Extensive ulceration of the intestines may be the factor which produces high blood concentrations. For these reasons the patient with dysentery should be given sufficient fluids to maintain a urinary excretion of 1500 cc per day or more in adults and comparable amounts in young children. If vomiting is present, isotonic salt solution, one-sixth molar lactate solution or 5 or 10 per cent dextrose solution may be employed.

Diet. During the phase of toxicity and active diarrhea a liquid diet containing large amounts of carbohydrate in the form of lactose or dextrose and rice broth should be given. Proteins such as gelatin or egg albumin can be given in solution. Felsen[1] recommends a "rice-banana-tea" diet which contains egg albumin water in addition to the named constituents. As soon as the patient is better, and particularly when hunger begins to return, a soft diet may be started, made up from the following list:

Carbohydrates
- Puffed rice, boiled rice, strained oatmeal, Cream of Wheat, toast, unsalted crackers, potatoes (baked or mashed)

Proteins
- Eggs (boiled or poached), stewed chicken, scraped beef

Dairy products
- Cottage cheese, butter, buttermilk and cream if well tolerated

Fruits
- Very ripe bananas, fruit juices

Liquids
- Tea, fruit drinks, broths, chicken, rice and noodle soups, creamed soups

The bland diet should be continued for about a week after symptoms have disappeared, after which the patient may gradually resume a normal diet.

Vitamin deficiency states are not likely to appear unless the disease has run a protracted course. In this event vitamins should be given parenterally, especially the vitamin B complex, until the diarrhea has

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disappeared and for forty eight or seventy two hours thereafter (Sometimes the abdominal cramps will continue to a lesser degree for three or four days after the diarrhea has stopped This should not cause alarm since they will disappear gradually without further treatment) Sodium bicarbonate should be given with either of these drugs 6 gm (90 grains) with the initial dose and 3 gm (45 grains) with each succeeding dose Rectal cultures should be taken on alternate days if this is feasible If not a culture should be taken after the temperature has fallen If the shigella organisms have not disappeared from the stool by this time a shift should be made to one of the poorly absorbable sulfonamides Among these succinylsulfathiazole is the preferred compound at the present time It should be given in doses of 10 gm (150 grains) initially followed by 5 gm (75 grains) every six hours in adults Children should receive doses in proportion to their weight This regimen should be continued until the rectal cultures no longer yield shigella or until several weeks try has made it apparent that the drug is not effective

Sulfamerazine may be substituted for sulfadiazine in identical doses Sulfathiazole is nearly as effective so that it can be used when the other two absorbable drugs are not available Phthalylsulfathiazole is probably as good as succinylsulfathiazole if similar doses are used In our hands another compound sulfacarboxythiazole[6] has also eradicated shigella dysentery More extensive trial of this compound is needed

When urinary excretion may be diminished and when patients cannot be watched closely for toxic manifestations as in soldiers in hot climates it may be desirable to use the poorly absorbable drugs during the acute stage of diarrhea If this is done the diarrhea must be checked immediately with opiates as otherwise the drug would be excreted too rapidly to be effective

A word might be added regarding those patients in whose rectal cultures no pathogenic organisms are found The sulfonamide treatment in these instances should be kept up until the symptoms have subsided or until some other cause for them is found since even with the best techniques *Shigellae* are not cultured from every patient with the disease

Specific Serum Many years of accumulated experience have proved the value of antidysentery (Shiga) serum against infections caused by this strain of dysentery bacillus No study has been made of its value when sulfonamides are also employed but the reasonable conclusion would be that in patients who have an infection with a Shiga strain and are extremely toxic both sulfonamides and serum should be given Doses of 10 to 100 cc diluted in 500 cc of isotonic salt solution should be given intravenously and repeated daily or more often until the toxicity is controlled The precautions regarding the administration of serum outlined on page 33 should be followed

16 *Brucellosis (Undulant Fever)*

The *Brucellae* are small gram negative rods which are often so short as to resemble cocci. There are three varieties: *Br. melitensis*, *Br. abortus* and *Br. suis*. While the first is usually found in infected goats and the other two are most commonly identified with cattle and swine respectively, *Br. suis* has also been found in cows and *Br. melitensis* in both cows and swine. Other animals which have been infected include sheep, horses, dogs, cats, rats and guinea pigs. Chickens and perhaps other birds are also susceptible.

Any of the three strains may infect man, producing the disease known as brucellosis or undulant fever and called by a variety of geographical names, the most common of which are Malta fever and Mediterranean fever. In this country most of the human infections are caused by the abortus and suis strains, melitensis infections being confined for the most part to the southwestern states. Infection is spread from cows and goats by the ingestion of raw milk and to a lesser extent through contaminated cream, butter and cheese. The disease is also contracted from swine and other animals and poultry as a result of direct contact with infected animals or meat. It is thus an occupational hazard among meat packing plant workers, farmers and veterinarians. Bacteriologists working with these organisms are also frequently stricken. Hardest to trace are the cases of those unwary individuals who consume infected raw milk during a short visit to the country.

By all the various modes of infection 1136 persons in the United States were reported by the U. S. Public Health Service to have contracted undulant fever in 1944. The actual incidence of the disease was undoubtedly much higher since these represent only the reported cases. The factor of contact with animals tends to increase the frequency of the disease in men as compared with women and to make the incidence higher during the more productive years of life, from twenty through forty five years of age.

Like typhoid fever, brucellosis is a generalized disease. It invades the entire reticulo-endothelial system and often involves other tissues and organs, particularly the bones and joints and the sex organs.

SYMPTOMS AND SIGNS

The *incubation period* varies considerably, usually falling within ten to fifteen days, although it has been recorded as anywhere from five to forty two days. In a typical case of the disease the patient com

subsided and it is evident that they will be well absorbed if taken by mouth

Treatment of Complications *Chronic or recurrent dysentery* should be treated by the extensive use of sulfonamides Either sulfadiazine or succinylsulfathiazole may be used If the response to an absorbable drug is not favorable a shift may be made to one of the poorly absorbable ones and vice versa Treatment should be continued until cure has been obtained as determined by cultural sigmoidoscopic and roentgenologic examinations Careful attention should be given to the use of a bland high caloric diet with added vitamins

Arthritis usually subsides with the acute phase of the disease If it lasts for several weeks or months longer as it occasionally does every attempt should be made to find out whether the patient is still carrying dysentery bacilli in the intestine and if so to eradicate them by the use of sulfonamides Otherwise the treatment of the arthritis is symptomatic

In other focal infections caused by *Shigella dysenteriae* such as endocarditis and meningitis streptomycin should be tried if the etiologic organism is sensitive to this antibiotic in vitro

Perforation intussusception and appendicitis should be treated surgically

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sweating more than usual and that the sweats are accompanied by weakness As the illness has progressed he has noticed afternoon fever preceded by chilly sensations or by chills

The frequency of the various symptoms and signs reported by Hardy[19] is shown in Figure 40 This frequency distribution of the individual clinical features of the disease is used in the discussion immediately following

Fever is characterized by two types of variation The difference between its lowest point in the morning and the height of the afternoon rise may be as little as one or two degrees or may be as much as four or five In addition the daily peaks gradually rise in a wavelike manner to a crest which is maintained for a period of one to several days Then they descend in the same manner to the trough of the wave The peak temperatures in the trough may be normal or may be one or two degrees above normal A few days to a few weeks later another wave appears and so on The waves remain approximately the same for many weeks or gradually reduce in height until they disappear entirely All patients do not show these undulations in fever Some exhibit a high temperature for a week or two followed by a rather rapid fall Others have a low grade fever lasting for weeks or months continuous or interspersed with periods of normal temperature

Sweating occurred in 84 per cent of the patients The sweats are characteristically profuse leaving the patient drenched weak and listless The perspiration has a peculiar odor which has been described as mousy There was a complaint of chilly sensations in 77 per cent of cases while frank chills were present in 37 per cent Headache and backache were complaints in 62 and 47 per cent of cases respectively General aching was present in 42 per cent of patients while pains in the back of the neck in the joints and in the abdomen were each present in approximately one-third of patients

Three fifths of the patients stated that they had no appetite and over half were constipated Vomiting diarrhea and distention on the other hand were seldom seen Nonproductive hacking cough occurred in 45 per cent of patients Other symptoms sometimes encountered in brucella infections are restlessness irritability emotional instability insomnia dizziness and palpitation Most patients lose weight gradually during the course of the disease

On physical examination the patient is likely to be alert mentally when seen at the time of day when the temperature is low but is frequently drowsy and apathetic if seen when the temperature is high An occasional patient will show slight enlargement of the lymph nodes Bronchial rales were heard in 10 per cent of Hardy s patients The spleen was enlarged in about one-third of his patients A variable amount of diffuse abdominal tenderness may be elicited in most patients at some time during the disease Sometimes local tenderness

ONSET — USUALLY GRADUAL

SYMPTOMS — THEIR FREQUENCE

WEAKNESS
SWEATING
CHILLINESS
RIGORS
PAIN: GENERAL ACHING, HEADACHE, BACKACHE, IN BACK OF NECK, IN JOINTS, ABDOMINAL
GI: ANOREXIA, CONSTIPATION
INSOMNIA
NERVOUSNESS
COUGH

SIGNS

FEVER
LOSS OF WEIGHT
PALPABLE SPLEEN
ABDOMINAL TENDERNESS
LEUKOPENIA

0 10 20 30 40% 50 60% 70% 80% 90% 100%

DURATION — AVERAGE TOTAL 3 MONTHS

Fig 40 Common clinical characteristics of *Brucella melitensis abortus* and *suis* infections (From Hardy Jordan Borts and Hardy Nat Institute Health Bull 158)

plains that over the course of several days or weeks he has become increasingly more tired and has developed aching pains particularly in the joints the back and the extremities He says that he has been

persist for some time after recovery. Carpenter[6] found that at the time the diagnosis of undulant fever was made the agglutinin titers of fifty patients were as follows:

Agglutinin Titers	*Number of Patients*
0	3
1:20 to 1:80	11
1:160 to 1:640	18
1:1280 and over	[illegible]

All observers agree that a few patients do not develop agglutinins *during the acute phase of the disease* and that *some never produce them*. A larger group exhibit only low titers, while the majority (in Carpenter's cases two-thirds) show agglutinins in titers of 1:160 or more. As in other infections, then, no arbitrary level can be designated which will always signify that brucellosis is present. Nevertheless, if the test is evaluated along with the clinical course, the diagnosis may often be made with reasonable certainty in the absence of a positive blood culture.

In the chronic stage of brucellosis the agglutinin titer tends to be lower than in the acute phase, although it still varies greatly from patient to patient. Evans[8] reported that among twenty-eight persons with chronic brucellosis 32 per cent showed no agglutinins and only 39 per cent had titers of 1:80 or higher. Since cross agglutination may occur between the *Brucellae* and other organisms, agglutination tests should always be run against *Past. tularensis*, *E. typhosa* and *S. paratyphi* at the same time. In general the organism showing the highest titer is the cause of the disease, although a definite decision in this matter should not be made until agglutination tests using all the suspected organisms are repeated several times and are considered in relation to a previous history of the disease or immunization.

Opsonocytophagic Test. This test consists in combining the patient's blood with live *Brucellae*, incubating for thirty minutes and then staining a film made from the mixture. The number of bacteria within the leukocytes are counted: the higher the number the greater the immunity. The procedure is complicated, and even Tovar's[14] discovery that formalin killed cultures of the organisms may be used does not make the test suitable for routine laboratory use. It is our opinion, as well as that of Carpenter,[6] Spink[13] and others, that just as much information can be obtained through other available tests.

Intradermal Test. When *Brucellae* or certain of their products are injected subcutaneously in an individual who is infected, or who has in the past been infected with these organisms, he may respond with a local reaction at the site of the injection. Preparations which may be used for this purpose include a heat killed suspension of *Brucellae* containing one or more strains, brucellergen prepared by Huddleson,[2]

attributable to the gallbladder or to the spleen will be found After they have removed the placenta by hand from an infected cow workers sometimes develop a rash on the exposed arm composed of discrete red maculopapules and accompanied by intense itching and burning Generalized rashes consisting of scattered macules not unlike rose spots have been found by some observers in a small percentage of patients

The Chronic Stage

After one or two relapses the disease sometimes burns itself out More often it smolders on breaking out in flames of fever every few weeks or months In some patients the fires burn low at all times with fever of one or two degrees or less nearly every day A certain number of patients apparently go into this chronic phase from the start of the infection although a careful history will often reveal even in these cases an episode of high fever and greater incapacity at some time in the past which marks the real beginning of the brucella infection

Some miserable creatures drag their way through many years of chronic undulant fever They are continually exhausted and complain of headache backache and pains in the muscles joints and extremities Without warning the fever flares up and they are prostrated in bed for several days after which they somehow manage to stagger around again until the next acute episode It is easy to see how these patients become tagged as psychoneurotics in fact it is difficult to comprehend how they can keep from acquiring a whole bundle of psychoneurotic traits The wonder is that all of them do not yield to the urge to put an end to their unhappy existence as indeed a few of them do

Laboratory and Special Examinations

Blood cultures may be positive at any time in the course of the disease regardless of the height of the fever In fact the organisms have been cultured from the blood during afebrile periods when there were no clinical evidences of the disease *Brucellae* are difficult to grow requiring special media and increased carbon dioxide tension for optimal results

Cultures of Other Material The organisms have been cultured from the stools from bile and from fluid obtained from joints Obtaining cultures from enlarged lymph nodes is another way in which the organisms may be found in doubtful cases

Guinea Pig Inoculation Material may also be injected into the groin of guinea pigs when cultures fail If the animal becomes infected agglutinins will appear and typical lesions of brucellosis will be found at autopsy This method often establishes a diagnosis when cultures fail although the answer cannot be obtained in less than two to five weeks

Agglutination Tests Agglutinins appear in the blood of most infected patients within one or two weeks after the onset and usually

patients should always be questioned as to whether previous skin tests for brucellosis have been performed

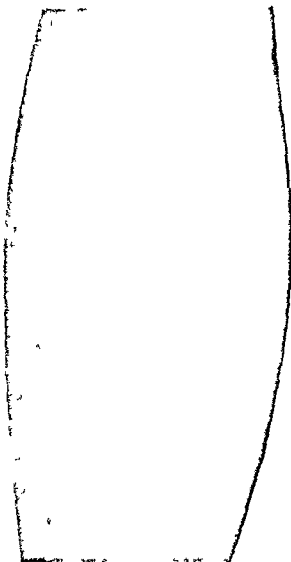


Fig 41 A positive brucellergen skin reaction (From Huddleson Brucellosis in Man and Animals Commonwealth Fund N Y)

Other Examinations of the Blood A complete study of the blood picture has been made by Calder[5] who found that leukopenia was present in the acutely ill patients whereas patients with the chronic form of the disease had leukocyte counts which were below normal

which is a nucleoprotein derivative of these bacteria and other fat free and purified protein antigens made from the organisms The first two are most frequently used When brucellergen is used 0 1 cc of the standardized extract is *injected* Only 0 05 cc *containing* 50 000 cells of the whole cell antigen should be used for the test injection since patients who are highly allergic to the bacteria develop a local slough when too many bacteria are deposited Readings are made at the end of two days and are definitely positive if there is an area of erythema and edema more than 2 cm in diameter (Fig 41) Another reading should be made on the fourth day after the test An indurated red area of any size remaining at this time should be considered positive even if the area was less than 2 cm in size at the end of two days Erythema and edema covering a small area should be considered as

TABLE 44

PERCENTAGE OF POSITIVE DIAGNOSTIC TESTS IN DIFFERENT GROUPS OF PATIENTS (COMPILED FROM EVANS[8] AND OTHER AUTHORS)

Disease		*Percentage of Patients with Positive*			
		Blood Cultures	Agglutination Tests	Opsonocytophagic Tests†	Intradermal Tests
Active brucellosis		69%	54%	16%	61%
Brucellosis in the past		0	29%	[illegible]1%	93%
No history of brucellosis	Ill with other diseases	0	5%	9%	14%
	Healthy subjects	0	0	0	11%

Titer of 1 40 or over considered positive
† Questionable and weakly positive tests not included

questionably positive while larger reactions especially if accompanied by systemic symptoms or sloughing are strongly positive

Brucellergen is preferable to the whole cell suspension because of the smaller chance of local necrosis Since Angle[3] has demonstrated that the vaccine gives a higher percentage of positive reactions than brucellergen if a skin test with the latter is negative it may be followed by a skin test with the whole cell suspension

When either a whole cell suspension of *Brucellae* or a preparation made from the organisms such as brucellergen is employed as a skin test it will usually produce agglutinins regardless of whether or not the patient is harboring a brucella infection Menefee[11] obtained agglutinins ranging from 1 80 to 1 1280 in 75 per cent of subjects within seven to twenty one days after they were given brucellergen intracutaneously It is obvious therefore that at least one agglutination test should be run before any intracutaneous tests are done and that

general invasion of brucella organisms involves the liver along with the other organs In some instances there are no clinical manifestations of this condition Most patients however exhibit some tenderness in the region of the liver and enlargement of the liver or even jaundice may occur One challenging concept which has been advanced is that cirrhosis may follow hepatic damage due to undulant fever Chole cystitis is present in an indeterminate number of patients *Brucellae* have been cultured from the bile by a number of investigators

Genitourinary System Inasmuch as *Br abortus* causes abortion in cattle and other animals we might expect the brucella organisms to affect the reproductive organs in humans also Abortion does occur in humans although from present evidence it seems to be infrequent The organisms have been isolated from the placenta and cases of salpingitis have been attributed to *Brucellae* Orchitis was found by Hardy in 5 per cent of his male patients He reported that it appeared during the period of invasion during the fastigium or during conva lescence that it lasted two weeks on the average and then subsided completely Epididymitis and prostatitis have also been reported Pye litis is occasionally found while nephritis is a rare complication

Nervous System Meningitis caused by *Brucellae* is characterized by an increase in the lymphocytes in the cerebrospinal fluid and the organisms have been cultured from this fluid in some cases Encephal itis myelitis and peripheral neuritis especially of the sciatic nerve have also been seen during undulant fever We should not overlook the profound depressions which sometimes seize these chronically afflicted patients and are so severe as to provoke some of the victims to suicide

Musculoskeletal System Joint disease is one of the distinctive features of undulant fever The joints are probably affected in most patients although the only clinical manifestation is aching A large proportion of these patients are found to have tenderness of the joints also In 10 per cent of Simpson s[12] cases the arthritis was the most prominent feature of the disease and the one which brought the patient to the physician Swelling of the joints or hydrarthrosis is infrequent having been observed in only 2 per cent of Hardy s cases Arthritis may be mono-articular or polyarticular Debono[2] reported the following joints to be involved in a series of 100 cases of *Br melitensis* infection

Joint	*Incidence* (per cent)
Ankle	40
Knee	33
Hip	25
Sacroiliac	25
Shoulder	0
Fingers	15
Elbow	10
Sternoclavicular	2

normal or slightly above normal The lymphocytes made up more than 30 per cent of the white blood cells in 76 per cent of the patients and more than 50 per cent in 17 per cent of the patients The percentage of polymorphonuclears was rarely increased above normal values and then only slightly In one fifth of the patients the eosinophils made up 5 per cent or more of the leukocytes Moderate acceleration of the sedimentation rate was present in slightly over one third of the cases Excessively fast rates could be explained on the basis of complications Mild macrocytic hyperchromic anemia was frequently found

Localized Infections and Complications

The failure to recognize the protean nature of brucellosis has been responsible for many mistakes in diagnosis The *Brucellae* obviously travel widely through the body and may develop in sufficient numbers in certain places to cause local infections It has already been pointed out that the lymphatic system is particularly attacked and that the spleen and lymph nodes are sometimes palpable The tonsils may be involved along with the other lymphatic structures This observation is of particular importance because the organisms can occasionally be obtained by culture from the tonsils Other systems will be considered below

Respiratory System Bronchitis is present in a large percentage of cases Hardy [10] for instance noted cough in one third of 175 patients some of whom had mucoid or mucopurulent sputum Examination of the chest in such cases usually reveals scattered moist rales Bronchopneumonia is a less frequent complication having been observed in two of Hardy s patients One patient developed a pulmonary abscess Lobar consolidation dry pleurisy pleural effusion and empyema have been encountered occasionally Although *Brucellae* have been cultured in rare instances from the sputum and empyema fluid of patients with respiratory complications in most cases they are not found and the pathological process must be attributed to the bacteria which commonly inhabit the bronchi

Cardiovascular System Endocarditis fortunately is a relatively rare complication although Spink[13] encountered two cases during a seven year period He states that an important diagnostic feature is the presence of bacteremia together with a high titer of agglutinins in the blood at the same time that the intradermal test is negative Any patient who has the clinical picture of vegetative endocarditis and whose blood persistently fails to show any growth when culture is done by the usual techniques should be studied with the possibility of brucella endocarditis in mind Hardy found endocarditis in 1 per cent of his cases One patient also had pericarditis

Gastrointestinal and Biliary Systems Hemorrhage due to intestinal ulceration has been reported but is exceedingly rare The

general invasion of brucella organisms involves the liver along with the other organs In some instances there are no clinical manifestations of this condition. Most patients however exhibit some tenderness in the region of the liver and enlargement of the liver or even jaundice may occur One challenging concept which has been advanced is that cirrhosis may follow hepatic damage due to undulant fever Cholecystitis is present in an indeterminate number of patients *Brucellae* have been cultured from the bile by a number of investigators

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Knee	33
Hip	25
Sacro iliac	[illegible]
Shoulder	20
Fingers	15
Elbow	10
Sternoclavicular	2

Patients with pain in the back should be investigated by means of roentgenograms for the possibility of spondylitis which Debono found in 4 per cent of his cases He states that radiculitis is a frequent accompaniment of vertebral involvement and that the entire condition resolves completely after a course of a few weeks in most instances The subject has been reviewed completely by Bishop[4]

Myositis has been cited as the cause of the many muscular pains from which undulant fever patients suffer One bit of evidence for this is the marked atrophy of muscles which sometimes follows the disease

Other Organs Ocular complications are fairly frequent Almost all the structures of the eye may be involved including the uveal tract the ocular muscles the cornea retina and the optic nerve

Otitis media mastoiditis and mastitis are other infrequent manifestations of the disease Phlebothrombosis sometimes results from a prolonged stay in bed just as in typhoid fever

Diagnosis

In an area where undulant fever is endemic physicians will be alert to the possibility that any fever whether high or low periodic sustained or undulant may be caused by *Brucellae* If generalized aches drenching sweats and arthritis are prominent manifestations and the patients do not appear so toxic or so drowsy as do patients with similar temperatures during the course of typhoid fever undulant fever is a strong possibility In urban areas particularly we must be on our guard not to miss these cases Patients with unexplained fevers should be questioned carefully as to the possibility of ingestion of raw milk whether on a recent vacation trip or during a past period of life on a farm or in a small town

When the diagnosis is suspected special tests are necessary in an attempt to verify it Unfortunately only the isolation of the causative organism can do this with certainty and that is difficult and takes considerable time Any cultural study will take at least one week and not until the end of the fourth week can a negative report be made with certainty An attempt may be made to culture *Brucellae* from the stool or from enlarged lymph nodes as well as from the blood Positive cultures have also been obtained from tonsils bile and joint pleural and cerebrospinal fluids Although splenic puncture has been recommended we feel that its value does not justify the danger involved As shown in Table 14 *Brucellae* have been cultured from the blood of about 69 per cent of patients with the disease This figure is higher than would be obtained in laboratories where the personnel was not accustomed to working with these organisms

The same table shows that an antigen titer of 1 40 or more was found in only 54 per cent of patients with the active disease and that

29 per cent of well patients with a history of brucellosis in the past and 5 per cent of patients ill with other diseases exhibited similar titers Obviously the agglutination test cannot be relied upon to make the diagnosis although it is true that in the acute disease high titers are often found and that such titers are more likely to mean that active disease is present Still there is no arbitrary figure the occurrence of which invariably indicates an active process An advancing titer of brucella agglutinins during a febrile illness would be strong although not conclusive evidence that the disease was undulant fever

A positive opsonocytophagic test is considered by some investigators to be a better indication than the agglutination test that the subject has attained immunity From the table it can be seen that the per centage of subjects in whom this test was markedly positive was only slightly higher among the group who had recovered from the disease than among those who were still ill Furthermore some patients ill with other diseases showed positive tests It seems evident that this test is less informative than the agglutination test For this reason we do not recommend its routine use

Skin tests with *Brucellae* or their products are more sensitive indicators of immunity being positive in 61 per cent of patients with the active disease and in 93 per cent of patients who formerly suffered from it Some individuals who gave no history of brucellosis on the other hand had positive tests Accordingly a positive skin test means merely that the patient has or apparently has had in the past a brucella infection and must be interpreted from this viewpoint

When a patient is suspected of having undulant fever we suggest that the problem be attacked as follows

1 Several blood cultures should be taken on successive days using the media and procedures which are most likely to grow *Brucellae*

2 Cultures of other fluid or of lymph nodes or stools may also be obtained

3 An agglutination test should be set up against *Brucellae* and at the same time against *Past tularensis E typhosa S paratyphi* A and *B*

4 If agglutination tests are negative or inconclusive they should be repeated in about five days If these in turn reveal nothing positive and there is sufficient time more agglutination tests should be done before a skin test is done

5 If all the above tests are negative an intracutaneous test should be done with brucellergen or a dilute suspension of *Brucellae*

If cultures are positive the patient has active brucella infection A patient who has symptoms characteristic of the disease and high ag glutinin titers may be presumed to have undulant fever If the titer is observed to rise during the course of the disease and to reach 1 1280 or more the diagnosis is almost certainly brucellosis If the titers

remain low or if the test is negative the patient may still have undulant fever A positive skin test in the presence of typical symptomatology strengthens this possibility

Differential Diagnosis Brucellosis is more likely to be confused with other generalized infections which have few or no localizing features These include typhoid fever tuberculosis influenza various bacteremias bacterial endocarditis malaria and Weil s disease

Although the patient with high fever due to *E typhosa* is usually more drowsy and toxic than the undulant fever patient and gastrointestinal symptoms and rash are less frequent in brucellosis this disease does sometimes closely simulate typhoid fever Diagnosis in these instances depends upon laboratory criteria Attempts should be made to culture the organisms from the blood and stools, and agglutination tests should be carried out against all the suspected bacteria Although some cross agglutination may occur the titer should be higher against the etiologic organisms

The diagnosis in miliary tuberculosis depends upon consistently negative cultures for *Brucellae* and repeated roentgenograms of the lungs to demonstrate tubercles or the discovery of tubercle bacilli in the sputum or elsewhere The more chronic and usually low grade fevers often found in brucellosis may simulate tuberculosis in the lungs or in foci elsewhere in the body Bacterial endocarditis and bacteremias will be detected if frequent blood cultures are done The diagnosis of malaria depends upon keeping this disease in mind and searching for *parasites Influenza is more of a problem since the laboratory diagnosis* of this disease is not at present a routine procedure Whenever the temperature of a patient remains consistently elevated for more than ten days or two weeks the diagnosis of influenza should be regarded with suspicion and other etiologic possibilities considered Weil s disease is characterized by a leukocytosis with an increase in the granulocytes Blood and urine should be inoculated into guinea pigs for identification of the leptospiral organisms

Because of the prominence of joint symptoms in many cases undulant fever may be confused with acute or chronic rheumatic fever with the arthritis which often accompanies gonococcic or meningococcic infections or with rheumatoid or even with osteo arthritis A careful history and observation over a long period of time may be necessary to differentiate these conditions unless gonococci meningococci or *Brucellae* are obtained on culture Gonococcic complement fixation tests will also be helpful

Pulmonary manifestations of brucellosis resemble bronchopneumonias of bacterial origin primary atypical pneumonia or pulmonary tuberculosis In the presence of abdominal pain and jaundice cholecystitis and liver abscesses must be ruled out. Appendicitis may also be difficult to differentiate Furthermore appendicitis sometimes occurs

during undulant fever If surgical intervention is a possibility the decision as to whether operation is necessary should be made on the same criteria that would be used if undulant fever were not present

In the differential diagnosis of diseases of the nervous system types of meningitis other than those caused by *Brucellae* can be differentiated only by examination and culture of the cerebrospinal fluid It is often difficult to distinguish the chronic phase of undulant fever from a profound depression or from hypochondriasis A careful psychiatric history together with laboratory examinations and skin tests for brucellosis is necessary to make the differentiation which even then is sometimes impossible

Hodgkin s disease deserves special consideration because of the recent demonstration by Wise[15] of brucella infection in fourteen consecutive cases of Hodgkin s disease In spite of the fact that they were obtained from patients who resided in an area where brucella infection is widespread cultures of sixty seven lymph nodes from patients not suffering from Hodgkin s disease were positive in only one instance Although this study is extremely interesting it has not been confirmed elsewhere The findings need further confirmation before the etiologic relationship of brucella infection and Hodgkin s disease can be established

Other diseases which may be confused with undulant fever are tularemia pyelitis and in the tropics kala azar

Prognosis

Considering the severity which the disease assumes at times and the tenacity with which it hangs on the case fatality rate is astonishingly low Eighty two deaths were reported in the United States during 1944 which represented approximately 2 per cent of all reported cases Because many of the milder cases undoubtedly escaped attention or were not reported the actual fatality rate is probably much lower than this

The prognosis for rapid recovery on the other hand is poor Few organisms can surpass the capacity of the *Brucellae* to induce exacerbations or to produce months and years of misery

Treatment

For the acute phase of the disease various measures are advocated These include specific antiserum sulfonamides and streptomycin Before attempting to evaluate these therapeutic agents it must be emphasized that brucellosis is a variable and capricious disease The bouts of fever even the highest ones usually subside spontaneously after a few days especially if the patient is resting in bed Moreover the disease may return days weeks or months later or in other cases not at all These vagaries must be kept in mind when it is asserted that a rapid decline in fever was the result of the therapeutic agent which

remain low or if the test is negative the patient may still have undulant fever A positive skin test in the presence of typical symptomatology strengthens this possibility

Differential Diagnosis Brucellosis is more likely to be confused with other generalized infections which have few or no localizing features These include typhoid fever tuberculosis influenza various bacteremias bacterial endocarditis malaria and Weil s disease

Although the patient with high fever due to *E typhosa* is usually more drowsy and toxic than the undulant fever patient and gastrointestinal symptoms and rash are less frequent in brucellosis this disease does sometimes closely simulate typhoid fever Diagnosis in these instances depends upon laboratory criteria Attempts should be made to culture the organisms from the blood and stools and agglutination tests should be carried out against all the suspected bacteria Although some cross agglutination may occur the titer should be higher against the etiologic organisms

The diagnosis in miliary tuberculosis depends upon consistently negative cultures for *Brucellae* and repeated roentgenograms of the lungs to demonstrate tubercles or the discovery of tubercle bacilli in the sputum or elsewhere The more chronic and usually low grade fevers often found in brucellosis may simulate tuberculosis in the lungs or in foci elsewhere in the body Bacterial endocarditis and bacteremias will be detected if frequent blood cultures are done The diagnosis of malaria depends upon keeping this disease in mind and searching for parasites Influenza is more of a problem since the laboratory diagnosis of this disease is not at present a routine procedure Whenever the temperature of a patient remains consistently elevated for more than ten days or two weeks the diagnosis of influenza should be regarded with suspicion and other etiologic possibilities considered Weil s disease is characterized by a leukocytosis with an increase in the granulocytes Blood and urine should be inoculated into guinea pigs for identification of the leptospiral organisms

Because of the prominence of joint symptoms in many cases undulant fever may be confused with acute or chronic rheumatic fever with the arthritis which often accompanies gonococcic or meningococcic infections or with rheumatoid or even with osteo arthritis A careful history and observation over a long period of time may be necessary to differentiate these conditions unless gonococci meningococci or *Brucellae* are obtained on culture Gonococcic complement fixation tests will also be helpful

Pulmonary manifestations of brucellosis resemble bronchopneumonias of bacterial origin primary atypical pneumonia or pulmonary tuberculosis In the presence of abdominal pain and jaundice cholecystitis and liver abscesses must be ruled out Appendicitis may also be difficult to differentiate Furthermore appendicitis sometimes occurs

If streptomycin is used the treatment should extend over a period of at least three or four weeks It is well to note also that at the present time such a course of treatment would be expensive Furthermore damage to the auditory nerve may occur if these doses are continued for more than three weeks

Vaccine Therapy The most controversial of all measures advocated for the treatment of brucellosis is the use of vaccines made of the whole organisms or culture filtrates made from them such as brucellin These agents are of no value in the acute stages and may be harmful Two different regimens have been employed in the chronic stage According to Huddleson[2] brucellin affects the course of the disease by producing a systemic allergic reaction which in turn is accompanied by a neutrophilic leukocytosis and an increase in immune opsonins He therefore advocates giving 0 1 cc of brucellin intradermally as the first dose If no marked systemic reaction occurs within twenty four hours doses of from 1 cc to 5 cc (the amount being proportional to the degree of reaction to the intracutaneous dose) are given intramuscularly at three day intervals with the purpose of producing systemic reaction Suspensions of the whole organisms have been recommended by others for the purpose of provoking a shocklike reaction It seems to us that this is a dangerous procedure and that the improvement in the patient which sometimes follows such treatment is more likely a result of the shocking effect of the foreign protein than a specific effect from the vaccine or filtrate employed

The method advocated by Harris[1] seems to us to be more logical and has been more successful in our own experience The standard vaccines containing 2 billion organisms per cc are diluted from 1 10 to 1 10 000 Intramuscular injections are started with small amounts of the 1 10 000 dilution and the amount increased progressively at three to five day intervals General reactions are avoided as much as possible If moderately severe or severe reactions occur the dose is reduced and later cautiously raised again

Fever Therapy Some patients with the chronic form of undulant fever respond well to a course of artificial fever therapy in a hot air chamber or similar apparatus (see page 233)

General Measures Patients with the acute form of the disease should be cared for in the same way as patients with other acute infectious diseases including bed rest sufficient fluids good nursing care and attention to elimination and body hygiene The treatment is similar to that given a typhoid patient (see p 2?0) except that the diet need not be free of roughage

The chronic stage of the disease will tax the patience and ingenuity of every physician It is necessary to follow the patient s symptoms without making him too conscious of them to be sympathetic without coddling and to give encouragement without raising false hopes

happened to be used last. Until the fever falls and the bacteremia subsides *permanently* in the majority of a large group of patients treated with a serum, drug or antibiotic, the physician should maintain a skeptical attitude as to its efficacy.

Specific Antiserums. A few patients have been treated with antibrucella serums with encouraging results, but such series have been small and the serums have not been available commercially.

Sulfonamides. Although the brucella organisms are sensitive to the sulfonamides in vitro, these drugs have not fulfilled their early promise of eradicating brucella infections in man. Practically all the sulfonamide drugs have been tried—sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine—with apparent success in some cases and with conspicuous lack of it in others. It is true that when sulfonamides are given to a patient in the acute phase of the illness the temperature begins to fall within a few days after treatment is started, but in the majority of cases the temperature would have behaved similarly if no specific treatment had been given. Furthermore, the incidence of relapse seems to be about the same in patients who receive sulfonamides and those who do not. Sulfonamides are of no value in the chronic stage of the disease and in our opinion of little value in the acute stage. Spink[13] believes that they help to control the bacteremia in *Br. abortus* infections. It is possible that they accomplish some measure of good by decreasing the number of bacteria in the body and by helping to localize them. It is doubtful that sulfonamides ever eradicate the infection completely.

Sulfonamides, if used, should be given in full therapeutic doses of 4 to 6 gm. initially and 1 gm. every four hours and should be continued for two or three weeks after the temperature has fallen to lower levels.

Streptomycin. Along with the many other gram negative organisms, the *Brucellae* are quite sensitive to streptomycin,[7] from 0.5 to 3.75 micrograms per cc. being required to inhibit their growth. Observations in the few patients who have been treated up to the present time make it seem likely that streptomycin does have a tendency to shorten the disease, although relapses have occurred afterwards.

Streptomycin should either be administered in doses of 3 to 4 gm. per day, divided into six or eight evenly spaced intramuscular injections, or preferably the sensitivity of the organism to the antibiotic should be determined and an amount given sufficient to maintain a blood concentration four to eight times that required to inhibit the organisms in vitro.

Pulaski[11a] has reported prompt subsidence of the activity of acute brucellosis in five of six patients treated with a combination of streptomycin and sulfadiazine. He recommends 0.5 gm. of streptomycin intramuscularly and 1 gm. of sulfadiazine orally every four hours for at least fourteen days.

17 The Acute Forms of Tuberculosis

Mycobacterium tuberculosis is a rod shaped bacillus which belongs to the group of organisms that once stained resist decolorization with acids or acid alcohols and are therefore called acid fast Three different types of tubercle bacilli have been found in warm blooded animals the human the bovine and the avian The bovine type infects cattle and other farm animals as well as humans The avian type occurs chiefly in birds It is found less often than the bovine type in swine and other farm animals and rarely if ever affects humans

The tubercle bacillus vies with the spirochete of syphilis in affecting many parts of the body and in producing the greatest variety of symptoms and signs Tuberculosis may be localized or widespread acute or chronic very mild or extremely severe To cover the disease in its entirety would require volumes We shall consider only the acute forms of tuberculosis which may be readily confused with other acute infectious diseases the primary tuberculous complex acute generalized miliary tuberculosis the acute forms of pulmonary tuberculosis tuberculous pleurisy and tuberculous meningitis The reader is referred to the books listed on page 327 for more complete information on the subject

The Primary Complex

In order to understand the variety of clinical syndromes which the tubercle bacillus can produce in the human body it is first necessary to consider what takes place after the primary infection in an individual not previously sensitized to the bacilli This condition has been studied particularly in children

When tubercle bacilli first gain access to the lungs they usually localize beneath the pleura in well ventilated portions of the lungs Some of the bacilli drain along lymphatics toward the regional lymph nodes which are usually located in the hilus This combination of a diffuse primary focus connected by lymphatics to the regional nodes is known as the *primary complex* and may also be seen in adults who have not previously been infected A similar picture may occur in other organs but less frequently The primary focus in children usually heals entirely leaving an area of fibrous tissue with or without calcification Sometimes however instead of primary healing the regional lymph nodes may caseate and the healing process is delayed or complicated The primary disease may on occasion also spread from the lymph nodes through the lymphatics into the blood stream or by rupture of a lymph node directly into a bronchus

Suggested Course of Treatment In the acute stages when there is high fever and toxicity streptomycin should be tried alone or in conjunction with sulfonamides

When the disease has been present for some time and the temperature is low or only moderately elevated vaccine therapy may be attempted according to the method of Harris[1] If this is unsuccessful artificial fever may be tried On the other hand if the patient is not having bouts of high fever and is able to obtain a reasonable amount of rest each day it is often best to use only general supportive measures in the hope that the patient s own resistance will overcome the disease

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(These two books are both complete monographs written from different viewpoints the former from that of a clinician and the latter from that of a laboratory investigator Since they complement each other both should be read by any one making an extensive study of brucellosis)

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by which it is performed are the intracutaneous (Mantoux test) and percutaneous (patch test) The former consists in injecting old tuberculin (O T) or purified protein derivative (P P D) The latter is more accurately measured and produces a smaller number of nonspecific reactions The dose employed is 0 1 mg of O T or 0 00002 mg of P P D It is injected intracutaneously into the forearm and read forty eight hours later A positive test consists in induration and redness of the skin occupying an area of 1 cm or more in diameter If the test is negative it should be repeated with 1 mg of O T or 0 005 mg of P P D

The patch test may be substituted for the first test with P P D or O T It has become popular because it is more convenient to use it eliminates the pain of the intracutaneous injection and at the same time it is of the same order of reliability The test is done by applying to the skin a strip of adhesive which contains one or two pieces of gauze saturated with tuberculin and another piece of gauze which contains no tuberculin for a control A positive reaction consists in a papular or vesicular reaction forty-eight hours later at the site of the tuberculin saturated gauze

The majority of persons with active tuberculosis respond positively to a test with the initial strength of P P D or O T or to the patch test Persons with an active tuberculous infection who fail to react to 0 005 mg of P P D or 1 mg of O T are either overwhelmed by tuberculosis or some other infection or are in the early stages of first infection tuberculosis and have not yet had time to develop a positive reaction

Once a person has developed a positive tuberculin reaction it almost always remains positive for life Consequently a positive test means only that the individual has had tuberculosis at some time and not necessarily that he has active tuberculosis at the time the test is performed On the other hand a small percentage of persons who have had a positive tuberculin reaction later become tuberculin negative The reason for this is not known

Diagnosis

The diagnosis of the phase of the primary complex or the first infection phase is usually made as a result of the discovery of tuberculosis in an adult in the child s immediate environment Sometimes on the other hand the child s symptoms first draw attention to the illness and in these cases the diagnosis is usually easily made if it is only considered When a young child is observed to have a positive tuberculin test a roentgenogram of the chest should be taken and adult contacts should be examined for the presence of active tuberculosis The mild syndrome which consists in a little fever and lassitude can be readily mistaken for the common cold or influenza If there is compression by the mediastinal nodes the symptoms may be confused with those of

With the establishment of the primary complex the patient develops allergy (tissue hypersensitivity) to the tubercle bacilli or certain of their products When this has taken place the tissues are more readily damaged by tubercle bacilli while at the same time they have an increased resistance to tuberculous infection The clinical evidence of this development of allergy is a change from a negative to a positive tuberculin test

Symptoms and Signs

Although the primary stage of tuberculosis may pass unnoticed in children careful observation often discloses a definite clinical syndrome Fever up to 102° F appears and lasts for a few days to two weeks and is usually accompanied by anorexia lassitude and general irritability Sometimes the clinical picture will be similar to that described under acute tuberculous pneumonia including the leukocytosis

Physical examination often reveals no abnormal signs or at most an area of partial dullness and diminished breath sounds Bronchial breathing is rare and rales if persistent are indicative of bronchogenic spread If the parenchymal lesion progresses sufficiently the usual signs of pulmonary tuberculosis appear

Complications

Pressure from greatly enlarged lymph nodes will cause cough which in some cases is spasmodic Wheezing or rhonchi may be present These symptoms may clear up in anywhere from a few days to several weeks or months Pressure of tuberculous abdominal nodes upon the intestinal tract may cause partial intestinal obstruction Rupture of a caseous lymph node into a bronchus results in massive tuberculous pneumonia in one area or scattered foci of tuberculosis throughout the lungs

Hematogenous spread may give rise to solitary foci in other organs or to acute disseminated miliary tuberculosis

Laboratory and Special Examinations

Though tubercle bacilli may sometimes be found in the gastric juice of a person with a primary complex it is particularly important to search for them in the probable adult source of the infection

Roentgenograms of the chest will usually show the primary lesion and the enlarged lymph nodes It is important to follow the course of the disease with serial x rays until one is sure that it has become quiescent

The change from a negative to a positive tuberculin test in a young child is taken as proof of the existence of the primary complex and is highly suggestive evidence of a recent infection from another (usually older) member of the household The tuberculin test is one of the most valuable aids in the diagnosis of tuberculosis The two common methods

SYMPTOMS AND SIGNS

Although the onset is sometimes abrupt it is more often gradual Chilliness fever general aching and malaise are the complaints which lead the patient to seek medical attention Anorexia was present in 90 per cent of Chapman s cases and weight loss in 85 per cent Evidences of pulmonary involvement were cough in 82 per cent of the cases dyspnea in 64 per cent chest pain in 19 per cent and hemoptysis in 15 per cent

The temperature curve shows no characteristic features Fever is usually irregular with considerable variation during the course of twenty four hours The pulse rate is often elevated in proportion to the degree of fever Depending upon the extent to which the lungs

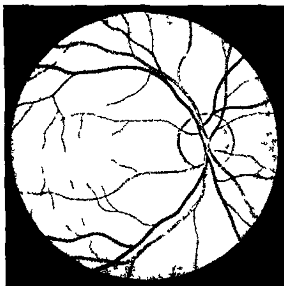


Fig 4. Miliary tuberculosis of the choroid (Koellner)

are affected the respiratory rate also may be considerably increased Toxicity is less than would be expected from the height of the fever

Many authors have grouped cases of miliary tuberculosis according as they are of the pulmonary meningeal or typhoid form depending upon whether the symptoms and signs point mainly to the lungs or to the meninges or whether the disease is characterized only by general symptoms as is typhoid fever While the physician may find that this classification helps him remember the variable characteristics of the disease he should bear in mind that all gradations between these syndromes may occur and that in an individual patient the disease may at one time in its course look like typhoid fever and at another time resemble meningitis or pulmonary disease

asthma pertussis or obstruction of a bronchus due to a foreign body The prognosis varies considerably depending upon the group studied The fatality rate is high when the primary infection occurs in very young children when food care sanitation and general living conditions are poor and when there is opportunity for repeated infection Among 472 children with primary tuberculosis in New York City[4] in whom all the factors just mentioned were unfavorable 25 4 per cent died of tuberculosis within a year On the other hand in children and adults in whom these factors are more favorable death is infrequent

TREATMENT

The only treatment is to make sure that the child receives adequate rest and nutrition until he is over the active stage of the primary infection Streptomycin has not been tried on patients in this stage of the disease except where serious complications have occurred

Acute Generalized Miliary Tuberculosis

When tubercle bacilli enter the blood invade various parts of the patient s body and produce multiple tuberculous foci along with symptoms of toxemia the process is called acute generalized miliary tuberculosis Some idea of its frequency may be obtained from Auerbach s[1] report that among 1656 persons with tuberculosis upon whom autopsies were performed 17 9 per cent had the acute miliary form of the disease This condition is found more often in persons who are more susceptible to tuberculous infection in general such as the Negro and the American Indian and particularly in the active phase of the primary infection in the younger age groups

The route by which the pathogenic organisms gain entry to the blood has been the subject of much discussion in the past In most instances the tubercle bacilli apparently drain from a tuberculous focus into the regional lymph nodes and thence through the lymphatic system into the venous system The bacteria may reach the blood stream as a result of the rupturing of a tuberculous focus into a vein or into the thoracic duct The organisms are discharged into the blood at intervals except in patients who die shortly after the first dissemination Multiple foci of varying sizes are the result Chapman[3] found that different organs are affected as follows

Organ	*Frequency of Involvement*
Spleen	100 per cent
Liver	100 per cent
Bone marrow	81 per cent
Lungs	63 per cent
Kidneys	53 per cent
Adrenals	42 per cent
Testicles	41 per cent
Ileum	33 per cent
Meninges	29 per cent

Diagnosis

Any patient who has high fever without definite localizing signs and symptoms or definite indications of another disease should be suspected of having acute miliary tuberculosis. A search should be made for tuberculosis elsewhere in the body and for tubercles in the choroid. *The sputum should be repeatedly examined for the presence* of tubercle bacilli. If the roentgenogram of the chest does not show the characteristic infiltration it should be repeated at ten day or two week intervals.

Diseases which may be confused with acute miliary tuberculosis *because of the similarity of the clinical pictures are* typhoid fever, subacute bacterial endocarditis and undulant fever. In certain other conditions the x ray appearance of the lungs may sometimes resemble that seen in miliary tuberculosis. Among these are Boeck's sarcoid, carcinomatosis of the lungs, coccidioidomycosis, pneumoconiosis, histoplasmosis and bronchiolitis fibrosa obliterans.

Prognosis

Only rarely does a patient recover from the acute form of the disease. In some patients small numbers of bacilli escape into the blood and *correspondingly fewer lesions are found in the various organs.* This is sometimes called subacute miliary tuberculosis. The prognosis in these patients is somewhat more favorable and the employment of streptomycin is altering the prognosis considerably.

Treatment

Treatment up to the present time has been entirely symptomatic. Preliminary investigations with streptomycin are showing encouraging results.[3, 4] Patients who respond favorably exhibit progressive disappearance of signs and symptoms and of roentgenologic manifestations *of the disease over a period of six to eight weeks.* Treatment consists in the intramuscular injection of 2 to 3 gm of streptomycin daily for two months divided into four to six doses.

Some of the patients develop tuberculous meningitis, which necessitates a modification in the therapeutic regimen (see p 326). In other *cases the tubercle bacilli become highly resistant to the streptomycin.* Another unfortunate complication has been the occurrence of a relapse in some patients after all evidence of the disease had disappeared and treatment had been stopped. Much more investigation will be necessary before it is possible to determine the optimal dose of streptomycin, the proper period of treatment and the prognosis in an individual case.

Physical examination of the lungs may reveal no abnormalities or there may be only a few subcrepitant or mucous rales found in a single area or in scattered ones In other cases only the signs of effusion may be present (pleural fluid was found in 30 per cent of Chapman s cases) while in patients with an original pulmonary focus the signs attributable to this are likely to dominate the picture

Other evidences of the widely distributed tuberculous lesions may be enlargement of the spleen and sometimes of the liver and the presence of choroidal tubercles The latter are pale grayish white oval or rectangular patches usually less than 1 mm in diameter (Fig 42) Generalized lymphadenopathy is an uncommon finding Amounts of *pericardial or peritoneal fluid sufficient to be demonstrable on physical* examination are likewise infrequent Meningitis occurs in about one-third of the patients The clinical features of this condition which usually dominate the picture when it is present are discussed under tuberculous meningitis (p 323)

Acute miliary tuberculosis terminates fatally usually within two weeks to two months of the onset Rarely is the course as short as a week or longer than six months

Laboratory and X Ray Examinations

The leukocyte count varies considerably from patient to patient It was below 5000 in 19 per cent of Chapman s cases between 5000 and 10 000 in 22 per cent and over 10 000 in 29 per cent The lowest count was 1600 and the highest 20 700 There was an increase in the neutrophils and a corresponding diminution in the number of lymphocytes *in 89 per cent of the patients* Although *Mycobacterium tuberculosis* is demonstrable in the sputum of only a small percentage of patients in the early stages sputum examinations should always be done since tubercle bacilli from a chronic pulmonary focus may be present and may be a source of infection to others Tubercle bacilli may sometimes be found in a smear or culture of the sternal bone marrow

The fact that the x ray examination of the chest presents a highly suggestive picture has led the clinician to depend upon it almost entirely for diagnosis Characteristically it shows hundreds of small areas of increased density which are not sharply outlined but merge into each other or into the surrounding tissue Unfortunately for purposes of diagnosis the roentgenogram of the lungs sometimes appears normal Reasons for this are (1) the lungs are not always involved (2) the lesions may not be large enough or compact enough to cause x ray shadows Sometimes the typical infiltration will be seen on later roentgenograms and sometimes death will intervene before they appear

Examination of the lungs may reveal the typical findings of lobar pneumonia although more frequently there will be diminished or absent breath sounds and moist rales instead Sometimes the physical signs are more indefinite and nothing may be heard except areas of moist rales This is particularly true of the bronchopneumonic form

Evidences of extrapulmonary tuberculosis may be found in the genitourinary or osseous system in the intestines or lymph nodes or elsewhere

Complications

Since tuberculosis may be found practically anywhere in the human body the possible complications are almost innumerable Those most commonly observed are pulmonary hemorrhage laryngeal tuberculosis tuberculosis of the intestines tuberculous meningitis and acute miliary tuberculosis

Course and Prognosis

Caseation excavation and spread to other parts of the lungs are characteristic features of acute tuberculous pneumonia Some patients will have so little resistance that death will take place within several weeks sometimes as soon as three weeks after the onset In others the disease may remain in an acute stage for weeks or months and then become subacute or chronic Rarely is there a crisis or lysis in seven to ten days such as there is in untreated pneumococcic pneumonia

Laboratory and X Ray Examinations

The leukocyte count is most frequently between 10 000 and 15 000 per cu mm It is rarely higher than 20 000 per cu mm and is sometimes within normal limits The percentage of polymorphonuclears increases somewhat but usually does not reach the heights attained in pneumococcic pneumonia Furthermore these cells contain few or no toxic granules Tubercle bacilli are almost invariably present in the sputum at least by the time it becomes profuse and purulent If they are not found on direct smear cultures or guinea pig inoculations should be done from concentrated specimens

Roentgenograms of the lungs will show consolidation usually of the lobar type involving all or part of a lobe Mottled infiltrations may be present elsewhere in the lungs and should be looked for since they are of great diagnostic value Rubin[9] has described the characteristic x ray appearance in the lobar type as follows opacity occupying all or most of an upper lobe the lower border being more or less sharply delineated by the interlobar fissure especially in its outer half Often the fissure is displaced upward Usually the opacity is densest in the region just above the fissure the density diminishing progressively

Acute Forms of Pulmonary Tuberculosis

Tuberculous infection of the lungs of some people creeps like a smoldering fire in low grass and in others it sweeps along with the speed and destructiveness of a forest fire The latter is the course of acute tuberculous pneumonia which results when a cavity or a tuberculous lymph node discharges its contents into a bronchus and thence into a wide area of the lung tissues of a person who has become highly allergic to tubercle bacilli It may sometimes be the result of the entrance of an overwhelming dose of tubercle bacilli into the lungs of a person who has not previously been infected with these organisms This form of the disease is most often found in young people in Negroes in diabetics and in other persons whose susceptibility to these organisms is great It is of particular interest because of the difficulty of differentiating it from other acute infections of the lungs particularly pneumococcic pneumonia Symbolic of the rapidity of the course of this condition is the frequently heard lay synonym galloping consumption or the more erudite phthisis florida

Pathologically the disease may take a lobar or a bronchopneumonic form The lobar variety occurs most commonly in the upper lobes Clinically it is difficult and relatively unimportant to make a distinction between the two forms In the involved area there is widespread caseation followed by destruction of the lung tissue with consequent excavation if the patient lives long enough

Symptoms and Signs

While the onset of the severe symptoms is usually sudden careful questioning will often bring out the fact that weakness and malaise preceded the acute symptoms by several days In addition many patients will be suffering from chronic pulmonary tuberculosis at the time the tuberculous pneumonia starts or will give a history of a previous tuberculous infection

The symptoms which make the patient seek the doctor are chilliness fever and cough The temperature may be no higher than 102° F but frequently reaches 104° to 106 F at some time each day Sputum may be scant and mucopurulent at first After a few days it is almost invariably copious frankly purulent and of a greenish or yellowish color In most instances there is no blood in the sputum When blood is present there will be streaking or profuse hemorrhage rather than the rusty color seen in pneumococcic pneumonia Respirations are rapid and the pulse is accelerated often out of proportion to the temperature Chills are occasionally seen at the onset Profuse sweating is common Pain in the chest is present in some individuals although it is seldom as severe as in other bacterial pneumonias Cyanosis is observed in an occasional patient It is not uncommon for the patient to lose several pounds a week while the disease is acute

diagnosis must depend however upon repeated examinations of the sputum for tubercle bacilli

Klebsiella (Friedlander) pneumonia is likely to be confused with tuberculosis because the consolidation may be lobar or diffuse and cavities may be formed if the patient remains ill for any length of time It must be differentiated by examination and culture of the sputum for tubercle bacilli and for *Klebsiellae*

Other bacterial pneumonias such as those caused by the beta hemolytic streptococcus by *H influenzae* by *staphylococci* and *P tularensis* can be diagnosed with certainty only by bacteriologic studies

Primary atypical pneumonia and the pneumonias caused by viruses of the psittacosis group and by rickettsia organisms may produce roentgenographic opacities which are readily confused with those of pulmonary tuberculosis The differentiation can sometimes be made only by comparing serial roentgenograms taken at intervals of a week or ten days The infiltrations change more rapidly and especially disappear more quickly in these pneumonias than they do in tuberculous pneumonia

Treatment

Complete bed rest is mandatory from the start After the acute phase has subsided pneumothorax is usually instituted if there has not been much destruction of lung tissues If however a considerable amount of destruction has occurred thoracoplasty is preferable Some clinicians believe that even during the acute stage if the disease progresses in spite of bed rest pneumothorax should be initiated even though the results to be anticipated may not be too favorable Some workers have advocated pneumoperitoneum and phrenic nerve crush while others believe that these procedures should be deferred until there has been some degree of improvement

Streptomycin has been used successfully[3, 4] in pulmonary tuberculosis It remains to be seen how well it will work in acute tuberculous pneumonia Because of its suppressive action on *Mycobacterium tuberculosis* this antibiotic may convert the acute into a subacute phase and thus insure better results from rest or collapse therapy

Acute Tuberculous Pleurisy

Tubercle bacilli reach the pleura in most cases by direct extension from a lesion in the underlying lung and occasionally by way of the lymphatics or blood stream The inflammation is characterized by congestion of the pleural blood vessels and the formation of a superficial layer of fibrinous exudate (fibrinous or dry pleurisy) In most instances pleural fluid also forms (sero-fibrinous pleurisy) The quantity of fluid varies from a few to several hundred cubic centimeters

toward the apex and periphery of the lobe At a later stage of the disease the density may not be homogeneous but may be scattered through the lobe

Diagnosis

The sudden onset of chilly sensations high fever and cough accompanied by signs of pulmonary consolidation should make the physician think of tuberculous pneumonia if one or more of the following features are present (1) the patient is suffering from or has previously had tuberculosis (2) several days or more of malaise preceded the acute symptoms (3) the patient does not improve within a week or ten days if treated symptomatically or within forty eight hours of the commencement of adequate penicillin or sulfonamide therapy and (4) the patient appears subjectively better than one would expect from the height of the temperature Suspicion of tuberculosis should lead to repeated examinations of the sputum for tubercle bacilli and a search of the roentgenogram of the lungs for evidences of cavitation or of old foci of tuberculosis

Differential Diagnosis Pneumococcic pneumonia is similar to acute tuberculous pneumonia in many respects Points of difference are (1) Chills are frequent in pneumococcic rare in tuberculous pneumonia (2) Sputum is occasionally blood streaked and seldom rusty in tuberculous pneumonia whereas a rusty sputum is characteristic of the pneumococcic variety (3) Frank pulmonary hemorrhages are rare in pneumococcic pneumonia and point with a fair degree of certainty to tuberculosis when they occur (4) Pneumococcic pneumonia most frequently occupies the lower lobes while tuberculous pneumonia is almost always in the upper lobes (5) Toxicity dyspnea cyanosis pleural pain and herpes labialis are more characteristic of the pneumococcic variety (6) Leukocyte counts seldom exceed 12 000 to 15 000 per cu mm in tuberculous pneumonia whereas in the pneumococcic variety they may rise as high as 50 000 or more per cu mm (7) When the total leukocyte count is high in pneumococcic pneumonia the cells of the polymorphonuclear series approach 100 per cent of all the white blood cells In tuberculous pneumonia they are usually increased but not to that degree and there is less shift to the left in the Schilling index (8) If pneumococci belonging to Types I II V or VII are found in the sputum a pneumococcic pneumonia is most likely present The presence of tubercle bacilli indicates that the pneumonia is tuberculous except in the rare instance when pneumococcic pneumonia is superimposed upon a chronic tuberculous infection

Abscess of the lung closely resembles tuberculous pneumonia in its clinical features Nontuberculous abscesses are more frequently present in the lower lobes or in the lower portions of the upper lobes Definite

diagnosis must depend, however upon repeated examinations of the sputum for tubercle bacilli

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SYMPTOMS AND SIGNS

Some patients will give a history of prodromal symptoms for several weeks or months before the acute illness These include fatigue anorexia cough or slight weight loss *The first symptom of the acute disease* is usually pain of a pleural type sharp and sticking in character often severe from its inception or becoming so within the first few hours The most common site is the lower half of the chest anteriorly or laterally although it may be felt at any point over the thorax If the central portion of the diaphragmatic pleura is involved the pain will be referred to the area above the clavicle in the neck or along the upper border of the trapezius Inflammation of the pleura covering the peripheral two or three inches of the diaphragm anteriorly and laterally or the posterior third of the diaphragm will produce pain over the lower thorax epigastrium lumbar region or even the lower abdomen The pain is thought to be due to inflammatory edema of the nerve endings It is aggravated by deep breathing coughing and sneezing and sometimes also by movements of the trunk The breath is taken in short rapid gasps in order to avoid the discomfort of deep breathing

The temperature frequently rises abruptly with the onset of the pain although the disease is seldom ushered in by a chill The peaks of the temperature curve are between 101° and 103° F in most cases with a daily remission of about two degrees Occasional patients will have a temperature as high as 105° F Others will have only a low fever or none at all Toxicity is absent or minimal

On physical examination a friction rub or pleural crepitus will be heard in most cases of dry pleurisy If a sufficient amount of fluid is present the characteristic signs of fluid will be heard and the pleural rub will be absent Quantities of pleural fluid less than 500 cc can seldom be detected by physical examination

COURSE

Acute fibrinous pleurisy ordinarily lasts only a few days to a week or two On the other hand when fluid is present the course is usually longer *Unless the fluid is aspirated complete resorption may not take* place for from three to six months in some cases During this time although the patient may be somewhat restless and lack appetite he is not acutely ill except in the rare instances when there is associated extensive tuberculous disease If the appetite is extremely poor several pounds may be lost Otherwise there may be no change in the weight The temperature subsides gradually from the onset in mild cases In others it remains elevated for several weeks before it starts downward

Recent bronchospirometric studies have disclosed that inflammations of the pleura which result in varying degrees of fibrothorax lead to a considerable decrease in pulmonary function which is apparently permanent

LABORATORY AND X RAY EXAMINATIONS

In cases of uncomplicated dry pleurisy fluoroscopic or x ray examination of the chest will reveal little Roentgenograms should always be taken however and repeated at six month intervals for the next three years to exclude the possibility of pulmonary tuberculosis

In the case of pleurisy with effusion roentgenograms help to determine the position and quantity of the fluid present In some instances fluoroscopy or roentgenograms are needed in order to discover the presence of fluid especially *if it is small in amount is confined to an* interlobar space or is pocketed elsewhere Fluid may be missed even if a roentgenogram is taken especially if a posterior anterior plate alone is taken In suspicious cases where fluid cannot be visualized in this position an x ray picture should be taken with the patient in the lateral decubitus position Repeated roentgenograms every six months over a period of three years should be taken and the patient should be observed carefully during this period for evidences of parenchymal tuberculosis

The fluid withdrawn is characteristically thin and straw colored and has a tendency to clot The specific gravity is less than 1 015 the protein less than 1 per cent and the cells are mostly lymphocytes Occasionally the fluid is hemorrhagic Tubercle bacilli can seldom be found on direct examination of the fluid At least 300 cc should be centrifuged and the sediment should be cultured and inoculated into a guinea pig In a large percentage of cases the etiologic agent may be identified in this way although failure to find tubercle bacilli does not exclude the diagnosis of tuberculosis The sedimentation rate seldom remains within normal limits even in the mild cases When it is elevated it should be used as an index of activity and the patient s convalescence should be arranged accordingly

The blood leukocyte count is normal or slightly elevated The differential count may show a slight increase in the granulocytes or may be within the normal range

When a patient has pleurisy with effusion chest roentgenograms should be taken of all the immediate contacts

The tuberculin test should be positive at the inception of a case of tuberculous pleurisy A negative test is strong evidence against a tuberculous origin of the disease A positive test however does not prove that the effusion is tuberculous since the tuberculin sensitivity may have been due to a previous and now inactive infection

DIAGNOSIS

Pleurisy can be diagnosed in most cases on the basis of the history and physical signs although roentgenograms should be taken in all cases Pleurisy with effusion seldom develops in the course of pulmonary

tuberculosis When it does roentgenograms will be needed to show the presence and extent of the parenchymal lesions Once pleurisy is diagnosed the old dictum that pleurisy is tuberculous until proved otherwise is still an excellent rule This is especially true when effusion is present Every attempt should be made to find the tubercle bacilli but if these examinations are unsuccessful the disease should never theless be treated as if it were tuberculous in origin

Differential Diagnosis The pain of pleurisy may be confused with that occurring in herpes zoster tumors or cystic disease of the breasts pressure on intercostal nerves due to a protruded intervertebral disk or to arthritis of the spine myositis fractured rib spontaneous pneu mothorax pericarditis angina pectoris myocardial infarction sub diaphragmatic effusions cholecystitis and other abdominal diseases These can almost always be ruled out by a careful history and physical examination

Dry pleurisy may be caused by the following conditions as well as by tuberculosis pneumonia lung abscess pulmonary infarction neo-plasm in the lungs or other structures adjacent to the pleura Pleurisy with effusion may be encountered as a complication of pneumonia of pulmonary infarction and of neoplasms which involve the lungs and pleura

When a chill occurs at the onset when there is a high fever leuko-cytosis or blood tinged rusty or prune juice sputum pneumonia is the most likely diagnosis Pulmonary infarction may begin with sharp pain in the chest with cough and expectoration of blood streaked or bloody sputum or the onset may be insidious with fever which may or may not be accompanied by chest pain and cough A condition which predisposes to pulmonary infarction (such as congestive heart failure peripheral or pelvic venous thrombosis or an operation) is usually found if carefully looked for

Pleurodynia occurs in epidemics and is characterized by the sudden onset of pain accompanied by fever general aching headache and malaise The temperature falls after a day or two and may exhibit a second and even a third rise within the next few days A pleural friction rub is heard for a brief period of time in a small percentage of patients

When pleural effusion is present it is often difficult to determine whether the disease is tuberculous or is due to other causes These include neoplasms congestive heart failure pneumonia cirrhosis of the liver and chronic nephritis Among the diagnostic measures which may be used for differentiation are postero-anterior lateral and oblique roentgenograms culture and guinea pig inoculation of the pleural fluid for tubercle bacilli and examination of the fluid for malignant cells The latter may be accomplished by sectioning the centrifuged sediment and examining it as if it were a tissue section

PROGNOSIS

Patients will recover from tuberculous pleurisy whether dry or serofibrinous unless there is extensive tuberculous infection in the lung or in other organs which changes the prognosis or unless rapidly advancing parenchymatous tuberculosis develops during the course of pleurisy

Even when there are no demonstrable lesions of pulmonary tuberculosis tuberculous lesions develop in the lungs during the ensuing five years in about one third to one half of patients with pleural effusion Although the percentage of patients who subsequently develop the pulmonary form of the disease is greater when tubercle bacilli are obtained from the pleural fluid pulmonary lesions also develop in patients in whom a tuberculous etiology could not be definitely established

TREATMENT

Rest Complete bed rest is required in dry pleurisy for the duration of the signs and symptoms *and for at least one week afterward If the* sedimentation rate reaches normal values and remains there the patient may be allowed to return gradually to his normal activities over the course of the next week or two

Serofibrinous pleurisy is likely to represent a more extensive process and requires strict bed rest for at least three months or longer if the fever and the fluid do not disappear within the first two months After the period of complete bed rest the next three months should be spent in gradual restoration to normal activities The sedimentation rate should also be used as a guide in these patients

Thoracentesis The chest should be tapped whenever the presence of fluid is diagnosed or suspected and as much fluid removed as can be aspirated This procedure should be repeated as significant amounts of fluid reaccumulate It is customary to inject a small amount of air after the fluid has been withdrawn so that it will be easier to establish a therapeutic pneumothorax later if it is needed Sometimes one aspiration is sufficient for therapeutic purposes sometimes several are required Rarely are more than five or six needed during the entire course of the illness

Tuberculous Meningitis

Tuberculous infection of the meninges results from the formation of caseous tuberculous foci in the substance of the nervous system in the meninges or adjacent structures and from the discharge of bacilli from these foci into the cerebrospinal fluid [7] It is more frequently observed in children between the ages of two and ten years and occasionally also in adults Pathologically considered tuberculous meningitis involves especially the base of the brain a location which favors

an increase in intracranial pressure and irritation and compression of the cranial nerves in this area

Symptoms and Signs

The onset is insidious and the first symptoms may be obscured by symptoms of tuberculosis elsewhere in the body or may pass unnoticed for weeks and months When a detailed history is obtained it is found that the patient has been tired and irritable and has had a slight degree of fever for a considerable period of time before the symptoms referable to the central nervous system made their appearance The most diagnostic signs and symptoms when they do appear include headache vomiting convulsions and strabismus

Examination shows rigidity of the neck and usually also of the entire back The deep reflexes are commonly increased the Kernig sign and the Babinski and equivalent reflexes positive Ophthalmoscopic examination may reveal edema of the disc and retinal tubercles Partial or complete paralysis of the cranial nerves may be detected particularly the oculomotor abducens facial and auditory nerves

Laboratory Examinations

The characteristic features of the cerebrospinal fluid as reported by Merritt[5] from a study of eighty four cases of tuberculous meningitis are shown in Table 45 It is evident from this that in the typical case the cerebrospinal fluid pressure will be increased there will be a moderate leukocytosis with lymphocytes predominating the protein content

TABLE 45

Characteristic Features of the Cerebrospinal Fluid in Tuberculous Meningitis

Examination	*Typical Findings*	*Extremes*
Pressure (mm of water)	Over 200	35 to 800
White blood cells (per cu mm)	25 to 500 (Lymphocytes predominating)	5 to 2021
Protein (mg per 100 cc)	45 to 500	25 to 1142
Sugar (mg per 100 cc)	Below 45	Less than 5 to 59
Chlorides (mg per 100 cc)	Below 650	441 to 732

From Merritt[7]

will be increased and the sugar and chloride content decreased Fluids which do not conform to these criteria are almost always found early in the course of the disease Specimens obtained later will fit into the expected pattern Characteristically the fluid is clear with a slight yellow tinge and forms a fine fibrin clot if it is allowed to stand The colloidal gold curve is usually either normal or raised in the midzone

Every attempt should be made to find the bacilli in a stained smear This can be facilitated by the use of some reagent to concentrate the bacteria The method which has proved most satisfactory in our experience is that described by Hanks[3] as follows

1 To each 2 cc of spinal fluid add 0 05 cc (or 3 drops) of chloroform and shake violently for ten minutes
2 Centrifuge at top speed for five minutes discard supernatant fluid
3 Smear the entire sediment without added fixative fix by heat stain with carbolfuchsin and decolorize and counterstain for five minutes in a 1 5 dilution of Gabbett s solution

A thorough search should yield the organisms culture of the fluid and inoculation of guinea pigs should result in the demonstration of the tubercle bacilli in nearly every instance

Diagnosis

Tuberculous meningitis is a strong possibility when signs of meningeal irritation appear in a person exposed to or suffering from tuberculosis Since signs of meningeal irritation should always lead to lumbar puncture in any event the cerebrospinal fluid findings are of the greatest importance

Other findings helpful in the diagnosis are the presence of tuberculosis in other parts of the body and a positive tuberculin test The latter is of course of more significance the younger the child Sometimes in severely ill patients the tuberculin test may be negative

Differential Diagnosis In acute syphilitic meningitis the cerebrospinal fluid findings often resemble those in tuberculous meningitis except that the chloride values in the former rarely fall below 650 mg per 100 cc A positive serological test for syphilis should verify the diagnosis except in the occasional patient who has a syphilitic infection in addition to tuberculous meningitis Occasionally however a false serologic test for syphilis may occur as a result of a tuberculous infection

There are several conditions in which the cerebrospinal fluid may resemble that found in tuberculous meningitis except for normal sugar and chloride values These include acute anterior poliomyelitis benign lymphocytic choriomeningitis encephalitis mumps meningoencephalitis lead encephalopathy brain tumor brain abscess and lateral sinus thrombosis It is well to note however that excessive vomiting from any of these conditions may deplete the serum chlorides and thus produce a lowering of the cerebrospinal fluid chloride content

Other bacterial meningitides will ordinarily be easy to differentiate from the tuberculous variety by their acute course by the presence in many instances of infections elsewhere than in the meninges by the predominance of polymorphonuclear cells in the cerebrospinal fluid and finally by identification of the causative organisms

an increase in intracranial pressure and irritation and compression of the cranial nerves in this area

Symptoms and Signs

The onset is insidious and the first symptoms may be obscured by symptoms of tuberculosis elsewhere in the body or may pass unnoticed for weeks and months When a detailed history is obtained it is found that the patient has been tired and irritable and has had a slight degree of fever for a considerable period of time before the symptoms referable to the central nervous system made their appearance The most diagnostic signs and symptoms when they do appear include headache vomiting, convulsions and strabismus

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Monographs

Miller J A and Wallgren A Pulmonary Tuberculosis in Adults and Children New York Thos Nelson & Sons 1939
Pinner M Pulmonary Tuberculosis in the Adult Its Fundamental Aspects. Springfield Ill Charles C Thomas 1945
Rich A R. The Pathogenesis of Tuberculosis, Springfield Ill. Charles C Thomas 1944

Torula meningitis is accompanied by cerebrospinal fluid findings so characteristic of those found in tuberculosis that it must be differentiated by finding the organism in a smear or culture Fortunately this condition is rare

Prognosis

Although an occasional patient with a few scattered tubercles in the brain may have recovered for practical purposes it can be said that before the advent of streptomycin all patients with tuberculous meningitis died

Treatment

No treatment had shown the slightest promise before streptomycin was used While the number of treated patients at present is too small to allow any definite conclusions it is obvious that here as elsewhere this antibiotic exerts a suppressive effect upon *Mycobacterium tuberculosis* Several patients treated both by the intramuscular and intrathecal routes have apparently recovered from tuberculous meningitis although most of them had serious residua such as blindness deafness and muscular paralysis

Streptomycin should be administered intrathecally in doses of 50 mg at daily intervals for the first three to five weeks and at gradually increasing intervals up to twice weekly thereafter for a total of three or four months[7] It should also be given intramuscularly 1 to 3 gm a day at four hour intervals for the same period of time

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18 *Pertussis (Whooping Cough)*

BY

LEWIS K. SWEET

Whooping cough or pertussis is caused by a small coccobacillus *Hemophilus pertussis* also called the Bordet Gengou bacillus after its discoverers It is a small hemoglobinophilic ovoid bacillus much like *Hemophilus influenzae* though less pleomorphic It is nonmotile has neither a capsule nor flagella and is not a spore former It is stained by the ordinary dyes and is gram negative Leslie[19] has distinguished four agglutination types of which the smooth Phase I found usually in freshly isolated cultures has the highest antigenic potency The organism is agglutinated by the blood serum of patients convalescent from pertussis and the serum gives a positive complement fixation test during convalescence and after recovery

Pertussis is an acute infectious disease that is epidemic in nature and affects any nonimmune person It is much more common in infancy and early childhood with no natural postnatal period of immunity its incidence is maximal by the fourth year after which there is a fairly rapid decline until it is rarely encountered in patients above ten years of age It does occur however in a few adults even among those over eighty years of age Pertussis shows a definite seasonal variation with its greatest incidence in the spring and early summer though occasional cases may be encountered at any season

The pathology of pertussis is in most respects nonspecific The organisms usually are present in great numbers between the cilia in the surface mucosa of the trachea and bronchi causing a clogging and retardation of the normal ciliary action that frees these structures of mucus There are no other specific lesions though at postmortem examination there usually is evidence of laryngitis bronchitis or bronchopneumonia and engorgement of the tracheobronchial nodes Emphysema is often present as are petechial hemorrhages throughout the body particularly in the brain and meninges and under the conjunctiva Edema of the face and of the brain is found fairly often

Symptoms and Signs

There are four different periods in the course of the average case of whooping cough incubational catarrhal paroxysmal and convalescent These are not always distinct however and may merge in

sidiously from one to another so that it is difficult to delimit them in any given patient

The *incubation period* usually is between five and fourteen days though rarely it may be as short as two days or as long as a month The average incubation period is about one week There are no symptoms during this time

The *catarrhal stage* of the disease in most children lasts from one to two weeks though it may be short or prolonged The disease usually starts with the typical symptoms of a common cold the manifestations being cough coryza sneezing and lacrimation There may be moderate malaise and a slight elevation of temperature The cough is not paroxysmal in nature It usually is worse at night though it may occur with considerable frequency at any time of day The cough is persistent however is resistant to treatment and becomes progressively more severe The appetite may be lost and vomiting is occasionally present

The *paroxysmal stage* of whooping cough is also variable in duration The average is about six weeks though it may vary from a few days to several months The characteristic feature is the cough which is usually worse at night and begins to come in distinct paroxysms There are considerable intervals free from cough during which the patient is quite comfortable Then when there is a cough it is explosive in nature There are from four or five to twenty or more expiratory coughs after a single inspiration The coughs continue until the patient exhausts his breath whether this be after one or two strong coughs or many lesser ones There is a pause from a few seconds to almost a minute during which the child struggles to inspire then the breath when it comes is drawn in forcibly through apparently tensed vocal cords with a long-drawn inspiratory whoop This train of events is repeated two to ten or more times in a single bout of coughing each repetition becoming more severe the period of apnea being longer and the inspiratory whoop longer and louder in many instances The patient becomes more uncomfortable with each succeeding paroxysm the intrathoracic and intravascular pressure apparently becomes greater and the face becomes suffused then congested and even purple The eyes show fright and confusion They are suffused and congested and tears stream from them Long strings of thick tenacious mucus hang from the nose The tongue may become swollen and purple and often protrudes during the cough At times the sphincters may relax allowing passage of urine or feces The coughing paroxysms may be so severe as to cause alarmed parents to fear that the patient is having a convulsion

After a number of increasingly severe paroxysms of coughing the typical patient will vomit The vomitus may contain food if the patient has eaten recently or it may consist only of thick stringy mucus

The coughing ordinarily ceases after the vomiting Then the child who has been sitting erect or leaning forward during the bout of coughing falls back exhausted covered with a profuse perspiration There then ensues another period of relative comfort and freedom from symptoms during which the child frequently sleeps

Young infants or children who are greatly debilitated may lack the strength to inspire with sufficient force to cause the typical whoop In such patients the nature of the seizure with several expiratory coughs after a single inspiration often with vomiting is quite as characteristic of pertussis as is the same cough followed by a whoop in older mo e robust individuals In these weak or debilitated infants the period of apnea after the cough may be most alarming The patient will be livid the inspiratory muscles may or may not appear to be working and death seems imminent In almost all children however the spastic glottis relaxes in time to allow respirations to start though in some instances syncope or even death may occur

The number of bouts of coughing varies greatly in individual patients In those with milder illnesses there may be only one or two a day often with only one or two individual paroxysms of coughing in each bout though in more severe instances there may be a severe bout every hour The average patient will have ten or twelve bouts a day

In older children there often is an aura or premonition of the impending paroxysm of coughing which causes them to try as best they can to avoid the inevitable cough This often is a sensation of dryness in the throat or of tightness in the chest though it may assume a variety of forms Frequently in a hospital ward a paroxysm in one patient will precipitate coughing of all the patients in the ward

During the paroxysmal stage in severe cases there often will be a constant suffused and edematous appearance of the face between bouts of coughing This is quite expressive of whooping cough and frequently suggests the diagnosis when no cough is heard Another occasional accompaniment at this time is subconjunctival hemorrhage This may consist only in petechial spots or there may be complete involvement so that the entire sclera is covered *with hemorrhage The cornea* however is unaffected Nosebleed is another common manifestation and petechial hemorrhages in other locations are encountered frequently

The cough is induced by a variety of mechanisms during the paroxysmal stage of pertussis Eating or drinking is regularly followed by coughing in many patients Any manipulation by the attendant is likely to induce a paroxysm Tickling the pharynx with a tongue depressor or an applicator usually will produce a cough though in many patients the cough is so inhibited by fright that this procedure fails In such patients the departure of the physician from the room usually

is a signal for a cough Where it is desirable to hear a cough for confirmation of the diagnosis or for demonstration purposes a short wait outside the room of the patient who has failed to respond to manipulation of the pharynx often is rewarded

The patient s general condition during the paroxysmal stage of the disease depends upon the extent to which the cough fear of the cough *and vomiting have interfered with nutrition* *If coughing or vomiting* is severe or if the patient refuses food because of fear of the inevitable cough there may be extreme malnutrition If the cough is controlled however the general condition remains good Fever is infrequent in the paroxysmal stage unless there is some complication

The *convalescent phase* of pertussis is the period when the coughing bouts become less frequent and less severe During this time all symptoms gradually decline *The cough continues to be more severe at night* but the days are relatively free from trouble The duration of the cough is extremely variable some children continuing to cough usually without vomiting for months after the attack A cold or other respiratory tract infection within six months and occasionally within a year after an attack of whooping cough is likely to be accompanied by a return of the paroxysmal cough

LABORATORY EXAMINATIONS

The *blood picture* in pertussis is quite characteristic There may be leukopenia early in the disease [27] but otherwise there is a leukocytosis with a relative and actual increase in the lymphocytes The leukocyte count in uncomplicated pertussis ranges from 12 000 to 30 000 with a differential count showing from 60 to 90 per cent lymphocytes This picture persists until late in the disease when there is a decline to normal levels or occasionally even below Also quite characteristic is the fact that the typical differential leukocyte count is maintained even in the presence of pyogenic infections With such a complication there often is *a marked increase in the total white blood count values of up to 100 000* per cu mm being common and up to 250 000 being recorded occasionally The blood count in such patients may be suggestive of leukemia but there is no anemia and the most immature lymphocytes are not present

Cultures may be taken by either of two methods When there is a *cough Petri plates of Bordet Gengou media* may be exposed at a distance of four to six inches from the lips for two or three to several coughs (depending upon the depth and force of the cough) Two or three plates are generally used This is the technique commonly employed and it gives positive results in a high percentage of early cases Recently however the nasopharyngeal culture has been introduced by Bradford [2, 5] By this method a small sterile cotton swab on a flexible copper wire is introduced through the nose until it touches the posterior nasopharyn

geal wall The swab is withdrawn and streaked lightly upon the culture medium The results by this method have been consistently better than those obtained by the cough plate [6, 22] Even better results are obtained when a small loopful of penicillin solution containing 1000 units per cc is placed on the culture medium the nasopharyngeal swab is passed several times through the penicillin solution and the plate is streaked with a long flexible wire loop With the penicillin technique 97 6 per cent of ninety five cultures from fifty two patients with pertussis were positive for *H pertussis* whereas only 76 9 per cent were positive when 0 85 per cent sodium chloride solution was substituted for the penicillin solution and simultaneous cultures were made [8] The penicillin technique is reported to be particularly advantageous during the catarrhal stage of the disease and in patients above two years of age

The Bordet Gengou bacillus rarely if ever enters the blood stream In consequence the blood culture is useful only in those patients with a complicating pneumonia or other pyogenic infection

Complications

The complications and sequelae of pertussis are chiefly of three varieties those caused by mechanical changes those due to infection and those of unknown origin

Complications Caused by Mechanical Changes Edema of the eyelids and face and petechial subconjunctival and nasal hemorrhages are probably caused by changes in pressure which occur during the paroxysm Umbilical inguinal or femoral hernias may also appear during pertussis or if present before may be greatly aggravated Prolapse of the rectum also may occur especially in malnourished patients Cardiac dilatation and emphysema are due to the same cause

Ulcer of the frenum is seen commonly in young children in whom the lower incisor teeth have erupted It is caused by mechanical irritation of the lower surface of the tongue as it is protruded and pressed against the teeth during paroxysms It usually appears as an oval ulcerated midline lesion It never appears before the paroxysms are well established and heals rapidly during convalescence

Vomiting may be due to the large amount of thick mucus in the stomach to the increased intra abdominal pressure from the severe cough or may be the result of gagging from the irritation of the pharynx by the cough It may precede although more often it follows the cough Diarrhea which is not uncommon in young infants may be due to the same causes Both these symptoms however may be due to parenteral or respiratory tract infection especially in infants with respiratory complications and may be quite serious in young patients

Complications Due to Infection These involve chiefly the respiratory tract The most frequent of these is otitis media which was present in 15 per cent of 100 consecutive patients with complicated pertussis

who were admitted to the Callinger Municipal Hospital A catarrhal infection with only injection of the ear drum often with more or less obliteration of the normal drum markings was found in thirty six (80 per cent) of the children with otitis media Purulent otitis media is rare with modern methods of therapy It occurred in only nine or 20 per cent of our patients with otitis media

Bronchitis and laryngitis are frequently encountered in pertussis In fact with the presence of *H pertussis* on the surface of the bronchial and laryngeal mucosa it is difficult to say when an uncomplicated pertussis ends and a complication begins If fever and rales are present however and the respiratory rate is increased during the paroxysmal stage of the disease a complicating bronchitis must be considered to be present

Bronchopneumonia is by far the most serious of the respiratory tract infections that complicate pertussis It may be due to *H pertussis* to the pneumococcus or to a mixture of organisms The incidence of complicating bronchopneumonia is hard to compute as only the more seriously ill patients are seen in hospital practice Rolleston[24] gives the incidence as 12 9 per cent among all the whooping cough cases admitted to the M A B hospitals between 1911 and 1914 Bronchopneumonia occurred in 63 per cent of our 100 patients with complicated pertussis It is much more frequently encountered in infants and young children than in older individuals and characteristically occurs during the height of the paroxysmal stage The onset is with fever and an increased respiratory rate The cough becomes more frequent but may be less paroxysmal in nature It still continues to be quite disturbing however Bronchopneumonia often is preceded by bronchitis As bronchitis merges into pneumonia the differentiation of the two conditions may be extremely difficult if not impossible

The findings upon physical examination are variable An extremely rapid respiratory rate up to 90 or 120 per minute is characteristic There is an inspiratory pause an expiratory grunt and dilatation of the alae nasi with each respiration This clinical finding recognizable from rather distant inspection together with a markedly elevated blood lymphocyte count is the most reliable diagnostic criterion in this condition Since the pneumonia is extremely diffuse and of an interstitial nature all the physical and x ray findings may be completely masked On auscultation and percussion there may be definite dullness with bronchial breathing and numerous crepitant rales or any or all of these findings may be absent Likewise the roentgenogram may show marked patchy infiltration or such diffuse changes that the chest seems to be clear There usually is an increase in the pulse rate to 150 or 180 beats a minute but this acceleration is by no means so marked as is that of the respiration The gastrointestinal symptoms especially vomiting and diarrhea usually are aggravated by the pulmonary infection

Lobar pneumonia is rare in pertussis It was found in only three patients in our group and constituted only 1 5 per cent of the pneumonias complicating pertussis It usually is caused by the pneumococcus The rarity of this condition probably is due to the fact that the patient s resistance to the spread of infection through the lung is lowered by the pertussis to the extent that the infection almost always spreads diffusely through the lung and results in bronchopneumonia Lobar pneumonia when seen is usually in an older child or an adult It is exceedingly uncommon as a complication of pertussis in infants and young children. Pleural effusion which was more frequent in those patients with pneumonia and pertussis before the advent of sulfonamide therapy is rarely seen now

Complications Due to Unknown Causes These are confined mainly to involvement of the central nervous system and are manifested during the acute attack chiefly by convulsions though sequelae such as spasticity blindness and mental retardation may persist after recovery [10] Convulsions formerly were thought to be due to cerebral hemorrhage but more recently a definite cerebral inflammation or edema has been demonstrated much more frequently than hemorrhage [15] Convulsions occurred in eleven of our 100 patients

Convulsions occurred during the course of bronchopneumonia in approximately half of these patients In the other individuals with convulsions the seizures developed after an attack of severe cyanosis which accompanied the cough Convulsions occur much more frequently *during the first two years of life In Habel s series*[15] *75 per cent of patients* with convulsions were in this age group The convulsive state may come on abruptly with a generalized seizure or it may be preceded by a period of somnolence and irritability during which there is slight twitching of the face or extremities This may last up to twenty four or even forty-eight hours before severe generalized clonic convulsions are manifest The convulsions may be unilateral bilateral or may alternate from side to side They may be short and recurrent or continuous When they are continuous death follows rather soon in most instances During the convulsions there is a general depression of the cardiovascular activity the pulse being rapid and thready often uncountable the skin flushed and the blood pressure depressed In other words shock often is a part of the clinical picture

Localizing neurological findings in infants are notably absent The deep tendon reflexes may be increased or depressed but there usually are no other neurological findings The cerebrospinal fluid usually is under increased tension and there may be a lymphocytic pleocytosis with a slight increase in proteins As a rule however the spinal fluid is normal except for the pressure changes The blood shows the marked lymphocytosis characteristic of pertussis or of pertussis and pneumonia

The presence of convulsions is a grave prognostic omen the *fatality rate* in patients with this complication varying from 50 to 80 per cent in most studies

Diagnosis

In the catarrhal stage the diagnosis is extremely difficult except when there is a history of contact and the organism is identified by culture

During the paroxysmal stage a clinical diagnosis can be made with reasonable certainty from a typical cough with a whoop or in very young or debilitated patients from a typical repeated staccato expiratory cough interrupting an expiration and followed by vomiting from the increased nocturnal severity of the cough and from a relative and actual increase of lymphocytes in the blood The presence of a sublingual ulcer is of considerable confirmatory importance

Differential Diagnosis Several conditions must be considered in the differential diagnosis One of the most important of these is the recently described entity of infectious lymphocytosis [22, 23] In this condition there is a marked increase in leukocytes with a differential count showing 70 to 90 per cent lymphocytes The condition is asymptomatic however or there are only mild general symptoms There is no cough suggestive of pertussis *Leukemia may be suggested in some patients* with an extremely high leukocyte count from an associated bronchopneumonia The pertussis patients however lack the anemia lymph adenopathy and other evidences of a primary blood dyscrasia including the presence of blast cells in the blood stream

A paroxysmal cough identical with that of pertussis may be caused by a foreign body in the larynx or trachea In this condition there is a sudden onset the symptoms show no diurnal variation and the blood picture is normal A similar cough may be caused by enlarged tracheobronchial glands pressing on the trachea The symptoms are of gradual onset however with no aggravation at night and the blood picture (except in those cases where primary blood disorders are causing the enlargement of the glands) is not characteristic of pertussis

The cough of early measles may closely simulate that of pertussis In measles however there is more coryza the blood shows a leukopenia and Koplik spots can be seen if they are searched for

Prognosis

The prognosis of pertussis depends primarily on the patient s age In infants under one year the disease is quite severe and the case fatality rate as reported by the older writers varied from 27 to 35 per cent [18, 24] With increasing age there is a lessening of mortality with rates of between 2 and 5 per cent for patients over five years of age Among well to-do

patients the mortality is much reduced at all ages The effect of modern therapeutic agents also has caused a great reduction in the mortality of pertussis Fox[14] reports only seventy five deaths 0 25 per cent among 29 815 patients in Milwaukee In this group there were fifty four deaths 2 4 per cent among patients under one year of age eleven or 0 4 per cent deaths among children between the ages of one and two and ten or 0 04 per cent among patients over two

PROPHYLAXIS

The prevention of pertussis has been the subject of extensive study in the past fifteen years The disease may be prevented or ameliorated either by the induction of active immunity or by passive immunity Active immunity is induced by the periodic administration of vaccines or antigens to susceptible individuals Successful pertussis vaccination was first performed by Sauer[26] who used vaccines made from freshly isolated strongly hemolytic cultures It is now recognized that vaccines made from phase I organisms of Leslie[19] are potent and are preferable to other antigens[9] Most vaccines contain 20 to 40 billion organisms per cubic centimeter and a total dose of 80 to 120 billion organisms is given[12] It is our current practice to give pertussis vaccine in combination with diphtheria and tetanus toxoids to infants seven to ten months old (see p 399 for the schedule of administration)

Recent experiences have indicated that newborn infants may be immunized against pertussis Sako gave a dose of 0 2 cc of alum precipitated vaccine containing 10 billion organisms per cc between the ages of two and twelve weeks with repeat doses of 0 3 cc and 0 5 cc each at four weeks interval with excellent results[25] A booster dose should be given at six to seven months of age Susceptibility to pertussis may be detected by the agglutinogen skin test recently introduced by Felton[11] A dose of one unit of acid extracted agglutinogen in 0 1 cc of isotonic salt solution is injected intradermally Immune patients react with an area of induration and erythema of at least 10 mm in diameter when read after an interval of twenty four hours Susceptible individuals show no reaction If the accuracy of this test is confirmed it will give physicians a much needed guide as to the immunity status of infants against pertussis

Passive immunity can be conferred by giving convalescent serum in doses of 20 to 40 cc shortly after exposure Much more satisfactory results have been obtained by giving hyperimmune human serum Two doses of 20 cc each are given intramuscularly spaced three to five days apart within two weeks after exposure Among 308 exposed infants so treated 78 6 per cent were protected Among 137 intimate and prolonged exposures in the home 67 9 per cent of the patients were protected[1]

Passive immunity has been conferred on the newborn infant by

vaccination of the mother between the sixth and eighth months of pregnancy by Kendrick and others Significant immunity as judged by the opsonocytophagic test was conferred upon the infants of thirty six out of fifty seven mothers vaccinated whereas similar immunity (titers of 1 101 or above) was found in the infants of only four of forty two nonvaccinated mothers[17] The duration of the antibodies in the infants was not studied by Kendrick but Cohen[7] found that no pertussis developed in eight infants whose mothers had been vaccinated between the sixth and eighth months of pregnancy if exposure occurred during the first six months of life but that pertussis developed after exposure during the second six months It is probable that if all mothers were immunized during pregnancy (or were given a booster dose if they had been immunized previously) immunization of the infant might be delayed until it reached an age of from four to six months

Treatment

The *general treatment* of the patient is of great importance in pertussis When there is no fever it is not necessary to keep the patient in bed In fact in good weather it is well to have him out in the open if he can be isolated from susceptible individuals If there is any fever however the patient should be kept in bed and should be given as much fluid as he can tolerate well During the paroxysms of coughing all patients should be well attended and should be given as much assistance as is possible Inversion of the young child to give postural drainage is helpful This is particularly true of young infants who are especially likely to aspirate vomitus or mucus and thus initiate a bronchopneumonia

Diet This is of particular importance It should be composed of easily digested nourishing food high in carbohydrate and protein and containing little fat If there is no vomiting except that which occurs at the end of a bout of coughing the food should be quite concentrated to reduce the bulk of the feeding Such food passes the stomach quickly This promotes absorption since it minimizes the loss from vomiting If there is a gastroenteritis however such concentrated foods should be avoided and only bland liquids such as broth skimmed milk tea or water should be given Of more importance than the quality of the food however is the method and time of feeding All children with pertussis should be given six or eight small feedings each day rather than three large meals Milk or milk drinks soups or other high caloric liquids may be used for some feedings If the meal is followed by a paroxysm of coughing and vomiting the child should be re fed within a quarter to one-half an hour provided he is not too exhausted to eat

Sedatives of some type are usually needed for patients with pertussis Oversedation should be rigorously avoided however as there must be

enough cough to clear the air passages of the mucus that collects in them Bromides chloral hydrate paraldehyde and ether in oil by rectum all have had their advocates In our experience however the most satisfactory sedative is phenobarbital When it is given twenty to thirty minutes before feeding it frequently allows a successful meal and at night it reduces the disturbance of sleep from an undue number of paroxysms It should be used in an initial dose of approximately 2 mg per kg of body weight ($\frac{1}{4}$ grain for fifteen pounds) every three or four hours The dose may be increased until it produces the desired effect or until the drowsiness of the patient warns of an overdose Larger doses may be used at night than are employed during the day time

Specific therapy of pertussis has been attempted along three lines There have been numerous attempts to treat pertussis by vaccines or endotoxin preparations after exposure or after the onset of the disease While these preparations still are in rather general use there is little definite proof of any beneficial results from them [8, 20]

Hyperimmune human serum which was suggested in 1933 by Jundell[16] and developed by McGuinness and his associates[21, 22] has been quite beneficial The minimum dose consists of three injections of 20 cc each given at forty eight hour intervals A fourth dose of 20 cc often is needed five to seven days after the third dose In severely ill patients especially those with pneumonia several intravenous injections of 50 to 100 cc are required Among 412 infants and children including 176 infants under six months of age and sixty in the second half year of life who were treated in this manner there were six deaths or 1 3 per cent [21]

Chemotherapy This has been employed since the introduction of the sulfonamide compounds in 1937 Sulfadiazine although partially effective in clearing the nasopharynx of *H pertussis*[4] has caused no dramatic shortening of the course of the disease Penicillin has been little used in pertussis as only occasional strains of the organism are sensitive to this antibiotic Its use has been limited largely to complicated cases usually those with pneumonia where it occasionally is much more beneficial than are the sulfonamide compounds

Streptomycin has been shown by Alexander[1] to be potent against the *H pertussis* In in vitro studies the organism is killed off by concentrations of streptomycin of from 3 to 5 micrograms per cubic centimeter This drug has had scant clinical application to date however Among fourteen rather seriously ill patients under seven months of age treated by us there was apparent improvement when doses of 25 mg were administered intramuscularly every three hours for five days There was rapid improvement in the clinical appearance of the patients accompanied by lessening of the vomiting and of the toxemia None of the patients has died Although the number and severity of

paroxysms were not recorded in these patients and the period of hospitalization was no shorter than that of twenty infants of the same age range with pertussis (all of whom recovered) the clinical impression is that streptomycin brought a definite amelioration of the symptoms in these patients It is suggested that larger doses may be more effective and may be essential in older patients

Treatment of Complications The two complications that merit special mention as regards treatment are bronchopneumonia and convulsions Since the bronchopneumonia may be due to the *H pertussis*

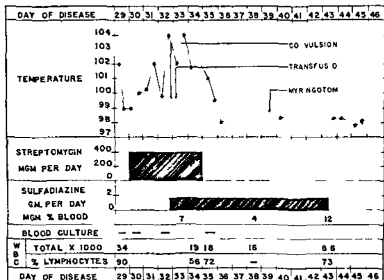


Fig 43 Temperature chart of a patient with pertussis and bronchopneumonia treated with streptomycin and sulfadiazine

A Negro infant aged eleven months entered the hospital on the twenty ninth day of pertussis with a complicating bronchopneumonia With streptomycin there was a temporary improvement but on the third hospital day he had a recurrence of fever and had a severe convulsion Sulfadiazine was started and a blood transfusion was given Convalescence was interrupted by otitis media and a parenteral diarrhea but recovery was ultimately complete

the pneumococcus or to a mixed infection no one agent or routine will suffice for all patients The general treatment should be carried out as for other patients with pneumonia Of specific benefit are the sulfonamide compounds especially sulfadiazine or sulfamerazine penicillin and streptomycin Because of the wider range of the organisms inhibited it has been our practice to give sulfadiazine initially to all patients with bronchopneumonia complicating pertussis in a dose of 70 mg per kg of body weight (½ grain per pound) initially and 145 mg per kg (1 grain per pound) for each twenty four hour period thereafter divided into six equal doses This may be given orally or

parenterally as indicated If there is no response within forty-eight to seventy two hours we have added penicillin in doses of 10 000 to 25 000 units every two to three hours by intramuscular injection In those patients in whom the pneumonia is due to the *H pertussis* streptomycin should be preferred to all other drugs We have used streptomycin in the treatment of six patients with pneumonia complicating pertussis Where doses of 25 to 50 mg every three hours were used there was no appreciable effect upon the disease (Fig 43)

With doses of 125 to 250 mg every three hours however there was a prompt drop in temperature in three patients treated In one

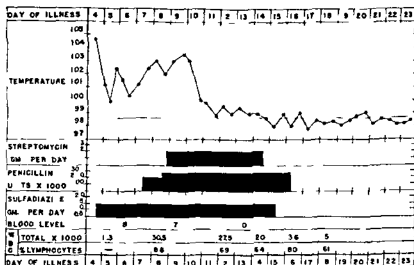


Fig 44 Temperature chart of a patient with pertussis and bronchopneumonia treated with penicillin and streptomycin

A Negro infant aged five month entered the hospital on the fourth day of illness with a cold and bronchopneumonia There was no response to sulfonamides or penicillin On the eighth day of illness the cough became paroxysmal and the hemogram was typical of pertussis The penicillin was increased and streptomycin was started The temperature became normal after sixty hour and convalescence was uneventful

of these patients (Fig 44) the pneumonia responded rapidly to streptomycin when penicillin and sulfadiazine had been given to no avail

Convulsions during pertussis constitute a definite emergency As pointed out by Habel[15] the treatment that offers the greatest benefit seems to be blood transfusion This is done as an emergency procedure in all such patients and it appears to offer considerable benefit The mechanism of its action is unknown and it is uncertain whether the use of blood plasma or albumin solutions to treat the shock would be of equal value Coincident with transfusions sedatives are used sparingly and then only the milder preparations such as bromides chloral hydrate or small doses of phenobarbital Morphine magnesium sulfate

and ether are so depressant that they are extraordinarily dangerous in this disease The pneumonia that is often present in the convulsive pertussis patient should be treated appropriately

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19 Hemophilus Influenzae Infections

Hemophilus influenzae is a small gram negative rod which sometimes grows in forms so short as to appear to be a coccus and at other times grows as a long slender bacillus Both forms as well as all the intermediates are commonly present in the same culture As the name *Hemophilus* indicates these organisms require some factor in blood (or in plant tissues) for growth *Hemophilus para influenzae* may be considered for all practical purposes to be the same organism as *H influenzae* Differentiation between them can be made only by the slight differences in their requirements for growth

The encapsulated strains which give smooth colonies on blood agar can be classified by the capsular swelling test into six types A through F These are the virulent strains and cause nearly all the human infections Type B is particularly virulent and causes over half of the severe infections in humans and over 90 per cent of the cases of meningitis The rough nonencapsulated strains are carrier types commonly found in the nose and throat of normal children and occasionally in those of normal adults Sometimes the rough strains are responsible for respiratory tract infections in adults

H influenzae infections are preponderantly diseases of children Fothergill[6] showed that the blood of adults is able to kill the virulent strains of these organisms while the blood of children between the ages of two months and three years seldom has this bactericidal property The blood of newborn infants is able to kill *H influenzae* as a result of antibodies acquired from the mother and the bloods of a gradually increasing percentage of children over the age of three years have this killing power These findings explain the age incidence of human infections Among 331 cases of meningitis caused by this organism which were collected from the literature 27 8 per cent occurred in children under one year of age 58 9 per cent in children one through four years of age and 7 9 per cent in children five through nine years of age Only 4 2 per cent of cases occurred in patients from ten through thirty nine years of age and 1 2 per cent in persons forty years of age or more

Hemophilus Influenzae Meningitis

The most frequent and most serious infection caused by *H influenzae* is meningitis The organisms apparently are transported from the throat or other parts of the respiratory tract to the meninges by way of the blood stream *H influenzae* is the third most frequent cause of

meningitis in children ranging behind the tubercle bacillus and the meningococcus.[6] When patients of all age groups are considered, the pneumococcus is the third most frequent cause of meningitis and *H. influenzae* the fourth.

Symptoms and Signs

An upper respiratory infection precedes the meningitis in about 60 per cent of cases. Less frequently, infection may be present elsewhere in the respiratory tract producing tracheobronchitis, pneumonia, sinusitis, otitis media or mastoiditis. While meningitis may be detected first by the occurrence of vomiting or stiffness of the neck, it frequently has an insidious onset. The latter type of case is most difficult to diagnose since there may be no symptoms except fever, undue irritability or loss of appetite and no signs except slight fullness of the fontanelles.

Initial symptoms observed in fifty patients were:

Vomiting	15 patients
Fever	13 patients
Headache	6 patients
Stiffness of the neck	5 patients
Anorexia	4 patients
Drowsiness or stupor	4 patients
General irritability	3 patients

As the disease progressed, forty-four of the patients developed nuchal rigidity, twenty-eight experienced vomiting, twelve had convulsions and eight were either markedly stuporous or completely comatose. Other symptoms were chills or chilly sensations, diarrhea, delirium and convulsions.

On examination, signs of involvement of the central nervous system are the most prominent. Bulging of the fontanelles will occur as a result of increased intracranial pressure. The Brudzinski, Kernig and Babinski signs are often positive. The condition of the deep reflexes is variable. They may be increased or decreased or may be within normal limits. Partial or complete paralysis of one or more of the cranial nerves may be seen. The third, fourth and sixth nerves are the ones most likely to be involved, with the production of strabismus. Paralyses of one or more extremities are occasionally seen. Backward bowing of the spine or opisthotonos may be present as a late sign in some cases, while in others it is never observed at any time.

Abnormal findings may be encountered outside the central nervous system. Petechiae are much rarer than in meningococcic meningitis. They were observed in only one of the fifty patients. When petechiae are present, they tend to be very small. Evidences of an upper respiratory infection, pharyngitis, otitis media or pneumonia may be present. Occasional patients are in shock when they are first seen by the physician.

LABORATORY EXAMINATIONS

The *blood leukocyte count* is usually elevated sometimes reaching high levels In our cases the white blood cells on admission to the hospital varied *from 8000 per cu mm* to *16 000 In 14 per cent of* the cases the leukocyte count was below 10 000 per cu mm while in 72 per cent it was over 15 000 per cu mm

H influenzae grew out in the *blood culture* in 70 per cent of twenty four cases in which the specimen of blood was obtained before the start of treatment

The *cerebrospinal fluid* yields the most significant information It should be examined as indicated on page 208 The fluid is usually under increased pressure and is almost always turbid The leukocyte count in fifty cases varied from 16 to 38 000 per cu mm as follows

Less than 100 per cu mm	2 cases
100 to 999 per cu mm	11 cases
1000 to 9999 per cu mm	24 cases
10 000 and above	13 cases

The polymorphonuclear cells varied from 54 to 100 per cent and were usually above 80 per cent of the total count. As in other bacterial infections of the meninges the protein content of the cerebrospinal fluid is usually increased and the concentration of sugar decreased

The organisms show up in the gram-stained sediment as small gram negative rods which may be confused with meningococci because of the coccoid forms The bacillary forms can always be found if the search is thorough Often they will be more readily identified in a smear stained with methylene blue If the organisms belong to Types A or B they will show capsular swelling when mixed with Type A or B *H influenzae* rabbit serum respectively The centrifuged sediment should also be cultured Blood agar is not so satisfactory for culturing *H influenzae* as chocolate agar or some other medium in which the blood is modified and mixed with agar

The spinal fluid can also be used for a precipitin test This consists in overlaying specimens of spinal fluid with Type A or B rabbit serum If bacteria of either type are present in the fluid the specific poly saccharide from the organisms should be precipitated by the serum of that type

Culture of the throat yields the *H influenzae* in 50 to 75 per cent of cases

COMPLICATIONS

Inflammations in the respiratory tract and associated passages have already been mentioned Tracheobronchitis and pneumonia will be discussed later as separate disease entities

Arthritis is encountered less frequently in influenzal than in menin

gococcic meningitis It is usually polyarticular Structures adjacent to the meninges may be involved Among the complications which result are thrombosis of the lateral sinuses abscesses in the brain osteomyelitis of the vertebrae hemorrhages in the retina and blocking of foramina through which the cerebrospinal fluid circulates with resulting internal hydrocephalus Fortunately all these are infrequent with present day treatment

A particularly distressing complication is the Waterhouse Friderichsen syndrome This is an acute fulminating form of the disease characterized by prostration and signs of peripheral circulatory collapse This syndrome occurs less frequently in influenzal than in meningococcic infections It is described more completely under the latter disease on page 207

Occasional cases of chronic *H influenzae* meningitis occur in which the disease lasts for weeks or months Low grade fever and signs of central nervous system involvement are present along with an increase in the number of cells in the spinal fluid The diagnosis rests upon the identification of the organisms and the treatment is the same as for the acute form

Diagnosis

Any combination of the following symptoms may be present in influenzal meningitis chilly sensations chills anorexia vomiting diarrhea irritability convulsions drowsiness stupor coma delirium *headache and stiff neck If symptoms referable to the central nervous* system are present if a positive Kernig or Brudzinski sign is elicited or if the fontanelles are bulging meningitis will be readily suspected and a lumbar puncture done It is in the cases where the fontanelles are not open or are not bulging and where the other characteristic neurologic signs are not present that the cerebrospinal fluid is not examined promptly and the opportunity for early diagnosis is thus lost Diagnosis in these patients is most difficult and requires the greatest acumen on the part of the clinician Often the only evidence of meningitis is the continuation of fever after apparently adequate chemotherapeutic or antibiotic treatment of otitis media pneumonia or other respiratory tract infections The clinician must be especially aware of the possibility of meningitis when an infant has periods of irritability alternating with drowsiness a high pitched cry or a vacant *look in the eyes*

If meningitis is suspected for any of the above reasons a lumbar puncture should be done This should yield the typical findings of bacterial meningitis increase in leukocyte count with predominance of polymorphonuclears an increase in protein and a decrease in sugar content Gram s stain of the sediment should reveal the gram negative pleomorphic cocco-bacillary rods If these can be typed directly by

the capsular swelling method or if a precipitin test on the spinal fluid is positive the diagnosis is at once made certain If immediate typing is not successful a tentative diagnosis can be made on the basis of the morphology and treatment can be started depending upon the outcome of the culture

If the cerebrospinal fluid does not exhibit the characteristic findings of meningitis and no other explanation of the illness emerges the physician should not hesitate to perform another lumbar puncture which may then reveal the typical features of the disease

Differential Diagnosis Conditions other than meningitis which may cause stiffness of the neck are listed on page 214 Other diseases of the nervous system which may be confused with influenzal meningitis are the meningitides caused by other bacteria virus and syphilitic infections of the central nervous system tetanus and irritation of the meninges resulting from an abscess or an infarct in the substance of the brain or spinal cord Tetanus can be diagnosed in most instances by the history or presence of a wound by trismus and convulsions and if doubt still remains by the absence of leukocytes and bacteria in the cerebrospinal fluid The other diseases of the central nervous system can be excluded only by a study of the cerebrospinal fluid In tuberculous meningitis and in syphilis and the virus infections of the nervous system (anterior poliomyelitis encephalitis mumps meningitis and meningo-encephalitis benign lymphocytic choriomeningitis and other rarer infections) the total leukocyte count is seldom above 2000 or 3000 per cu mm the predominant cell is the lymphocyte and the dextrose concentration is normal Exceptions to this are the predominance of polymorphonuclear cells in the cerebrospinal fluid in the early stage of poliomyelitis and the lowering of the dextrose concentration in tuberculous meningitis Bacteria will of course be absent in the stained sediment in all these conditions with the exception of some cases of tuberculous meningitis The other bacterial meningitides are differentiated by bacteriologic examination of the spinal fluid as well as by culture of the blood and other materials

Prognosis

Before specific treatment was available the case fatality rate approached 100 per cent As will be seen in Table 46 among the symptomatically treated patients of all ages the case fatality rate was 96 per cent The only patients who recovered were one in the age group of one through four years and three in the age group of ten through thirty nine years

In patients treated with specific therapeutic agents as well as in those treated symptomatically the disease is more severe in infants under one year of age and in the very old age groups The poor prognosis in the former patients is partially explained by Fothergill s[6]

TABLE 46

Case Fatality Rate in Patients with *H Influenzae* Meningitis According to the Age of the Patient and the Treatment Given

Treatment Given	Age of Patient (Years)									
	Less than 1		1 through 4		5 through 39		40 and over		All Ages	
	Patients Treated	*Died Per Cent*	*Patients Treated*	*Died Per Cent*	*Patients Treated*	*Died Per Cent*	*Patients Treated*	*Died Per Cent*	*Patients Treated*	*Died Per Cent*
Symptomatic only	34	100	59	98	16	81	2	100	111	96
Sulfonamides (except sulfadiazine)	12	83	42	57	9	33	1	0	64	58
Sulfadiazine*	35	40	69	12	13	8	1	100	118	20
Streptomycin†	16	31	30	10	3	0			49	16

* Alone or in conjunction with specific serum
† Alone or in conjunction with sulfonamides or sulfonamides and serum

findings as previously related that the blood of infants has little or no killing power against influenza bacilli except for that transmitted from the mother

Another factor related to the prognosis is the dextrose content of the cerebrospinal fluid The prognosis is poor when there is a low dextrose concentration We have observed no correlation between the outcome of the disease and the leukocyte counts in the blood or cerebrospinal fluid nor the presence or absence of bacteremia

A still better aid to prognosis is the determination of the number of organisms found per high power field in the stained smear of the sediment obtained by centrifugation of the initial specimen of spinal fluid When influenza bacilli are not seen in the smear and are obtained only upon culture or when less than one organism is present per high power field the prognosis is good When the bacilli average more than four per field the outlook for recovery is much worse Intermediate numbers of organisms indicate a fair prognosis

Even though the patient recovers sometimes incapacitating sequelae may remain These include monoplegia or hemiplegia which may clear up within several weeks or months or may be permanent hydrocephalus and idiocy These are seldom encountered in patients treated according to present day methods

Treatment

Specific Antiserum The first type of serum to be used extensively in the treatment of *H influenzae* meningitis was the immune serum made from horses by Fothergill He reported* an 81 6 per cent case fatality rate among 201 patients treated with this serum Later Alexander produced an antiserum by immunizing rabbits which has given excellent results although its usefulness cannot be completely evaluated since in most instances it has been employed in conjunction with sulfonamides This serum is available for *H influenzae* Type B which causes over 90 per cent of the cases of influenzal meningitis It is standardized according to the number of milligrams of antibody nitrogen present The intravenous route is used almost exclusively except in very young children who may be given the serum intramuscularly if it is impossible to enter a vein Intrathecal serum is not recommended

The need for further treatment may be determined by one of two methods Two hours or more after the serum has been administered the patient's serum may be tested for its ability to produce swelling of the capsule of the infecting organism A sufficient amount of antibody is considered to be present if a 1 10 or greater dilution of the serum will cause swelling The test is repeated during the active stage of the disease at twenty four hour intervals or more frequently if adverse symptoms appear If the antibody content is not sufficient to produce such capsular swelling additional serum should be given until

the proper titer is obtained The alternative is an intracutaneous test with a 1 10 000 dilution of Type B *H influenzae* polysaccharide[4] A positive test consisting of a wheal 10 mm or more in diameter surrounded by an area of erythema reaching its height within ten to thirty minutes indicates the presence of sufficient antibody in the blood

Sulfonamides Sulfadiazine has been shown by Alexander[2] to be definitely superior to sulfanilamide and sulfapyridine and probably superior to sulfathiazole and sulfamerazine when administered to mice infected with *H influenzae* This superiority is evident in human infections As shown in Table 46 the case fatality rate in 118 collected cases of influenzal meningitis treated with sulfadiazine was 20 per cent as contrasted to a 58 per cent fatality rate among sixty four patients treated with other sulfonamides Some of the patients in both groups received type specific antiserum in addition

The recommended dose of sulfadiazine is 0 06 to 0 1 gm (1 to 1½ grains) per pound of body weight for each twenty four hour period One half of this dose should be given initially by the intravenous route in the form of the sodium salt dissolved in a 5 per cent or less concentrated isotonic salt solution or one sixth molar lactate solution One sixth of the twenty four hour dose should be given every four hours thereafter by administering the crushed tablets or a solution of sodium sulfadiazine by stomach tube If maintenance doses of the drug are given by subcutaneous injection the calculated twenty four hour dose may be divided into three parts and administered every eight hours but the doses must be controlled by determinations of the concentration of sulfadiazine in the blood

Older children and adults who are not critically ill are best treated by the oral method entirely since the opportunity for the development of renal complications is considerably less when sulfonamides are not given parenterally Adults should receive 6 gm initially and 1 gm every four hours

Streptomycin Hewitt[7] found that the majority of strains of *H influenzae* are sensitive to 2 5 micrograms of streptomycin per cc and that all the strains studied by him were sensitive to 10 micrograms or less per cc Since these concentrations are easily obtainable in the blood after intramuscular administration and in the cerebrospinal fluid after intrathecal injection *H influenzae* infections should be amenable to treatment with this antibiotic Reports by Alexander[3] and by Weinstein[8] and our own clinical experience are in agreement with this The fatality rate among forty nine patients treated with streptomycin was 16 per cent

Because of the poor penetration of streptomycin into the cerebrospinal fluid it should be given by the intrathecal as well as by the intramuscular route The dose is from 0 025 gm to 0 05 gm once a

day intrathecally and 0.5 to 2.0 gm intramuscularly during a twenty-four hour period (Fig 45)

A complication of streptomycin therapy which has been reported by Weinstein[8] is the development of meningitis or pneumonia caused by the *Staphylococcus aureus*. This is apparently due to the inhibitory action of the antibiotic upon gram negative organisms which shifts the balance among the flora of the pharynx and thus allows the staphylococci to multiply and spread. We have likewise observed this phenomenon during streptomycin therapy. When such an infection is suspected search should be made for gram positive organisms by cul-

Fig 45 Temperature chart of a patient with *Hemophilus influenzae* meningitis treated with streptomycin

The patient J C was an infant two years of age in whom nausea vomiting and low grade fever developed one week before admission. Nuchal rigidity and weakness of the right leg appeared on the day of admission. Examination also showed a nasal discharge. In the initial specimen of spinal fluid leukocytes were seen, but no organisms. When the nuchal rigidity became worse and the child became stuporous intramuscular penicillin therapy was begun, but it produced no improvement in forty-eight hours. At this time the cultures of the blood and urine which had been taken on admission grew a Type B *H influenzae* and treatment was shifted to streptomycin. The temperature fell and the toxicity abated during the next forty-eight hours. Recovery was complete and the patient was discharged on the twenty third day after admission.

turing the pharynx sputum and cerebrospinal fluid; if they are found penicillin should be given in the doses recommended for those infections.

Penicillin Since nearly all strains of *H influenzae* are resistant to the concentrations of penicillin obtained in the blood by the usual therapeutic doses this antibiotic is not recommended.

General Measures Headache may be relieved with aspirin codeine or if necessary morphine. Delirium if it seems to be exhausting the patient should be treated with sedatives such as the barbiturates chloral hydrate paraldehyde or morphine. It is necessary to give large

amounts of fluids since these patients are almost invariably dehydrated If sulfonamides are employed a sufficient amount of fluid should be administered to restore hydration and to insure a normal output of urine

Suggested Schedule of Treatment 1 (*a*) When a tentative diagnosis of *H influenzae* meningitis is made streptomycin treatment should be started immediately in doses of 0 025 gm daily by intrathecal injection and 0 125 gm intramuscularly every four hours In patients over ten years of age and in all extremely ill patients 0 25 gm may be given intramuscularly every four hours Likewise the intrathecal dose may be 0 05 gm in patients who are very ill

(*b*) In view of the development of staphylococcic infections in patients treated with streptomycin alone the safest procedure is to give sulfadiazine to all patients in addition to streptomycin On the other hand if streptomycin is not available or if expense is a factor and the disease is mild treatment may be initiated with sulfadiazine alone Sulfonamide treatment should not be relied upon alone in patients under two years of age in those who are comatose or delirious or whose spinal fluids contain more than one bacillus per high power field

The dose of sulfadiazine whether used alone or in conjunction with streptomycin should be 0 03 to 0 05 gm ($\frac{1}{2}$ to $\frac{3}{4}$ grains) per pound of body weight followed by 0 06 to 0 1 gm (1 to $1\frac{1}{2}$ grains) per pound for each twenty four hour period divided into six doses at four hour intervals

(*c*) When the prognosis is poor at the onset 100 to 200 mg of specific rabbit antiserum should be given at the start of treatment along with streptomycin and sulfadiazine The presence of any of the following would indicate a poor prognosis

Poor general nutrition in an infant
Coma or delirium
Extreme toxicity
Nerve paralyses monoplegia or hemiplegia
The presence of more than three bacilli in the spinal fluid per high power field

2 Forty-eight hours after therapy has been started (or sooner if the patient appears worse) the condition of the patient should be re evaluated If the temperature has begun to fall if the general condition of the patient has improved if the cerebrospinal fluid no longer contains organisms and the dextrose concentration has increased the same therapy may be continued If these evidences of improvement have not appeared it is best to add serum if it has not already been given in doses of 100 to 200 mg of protein nitrogen If sulfadiazine alone was used from the start streptomycin should be added and if the prognosis appears very grave serum also

Furthermore by the end of forty-eight hours the streptomycin sensi

tivity of the organism obtained before the start of treatment should have been tested If the organism is resistant to more than 5 micrograms of streptomycin it is best to give serum in addition to streptomycin and sulfadiazine

Additional amounts of serum in doses of 50 to 100 mg of protein nitrogen may be given at daily intervals if the patient s condition requires or if the patient s serum in a dilution of 1 10 fails to produce swelling of the capsules of the causative organisms

3 If after initial improvement there should be a subsequent relapse as indicated by a rise in temperature not otherwise explained a considerable increase in the spinal fluid leukocyte count after it had reached normal or nearly normal limits or a return of *H influenzae* to the spinal fluid or blood serum should be given immediately and the dose of streptomycin increased in accordance with the in vitro studies on the sensitivity of the infecting organism

4 After the temperature has dropped to normal and remained there for four or five days after the patient s toxicity has decreased and after the dextrose concentration of the spinal fluid has returned to normal values and the bacteria have disappeared from this fluid and from the blood the administration of streptomycin and sulfadiazine may be discontinued Lumbar puncture should be repeated one week later and at weekly intervals thereafter (or sooner if there is any suspicion of a relapse) until the leukocyte count is below 30 per cu mm and all the other constituents are within normal limits

Treatment of Complications When purulent otitis media or sinusitis is present the etiologic organisms should be determined by culture whenever possible If the infection is due to *H influenzae* the therapy employed for the meningitis may be sufficient to take care of it If the infection is caused by other bacteria penicillin should be given in addition to streptomycin when indicated Surgical drainage may be needed in severe purulent infections

There is no treatment for paralyses of nerves monoplegia or hemiplegia other than the treatment of the general infection Improvement of these conditions may take place during the patient s hospital stay or may occur after months or even a year or two In other cases the paralyses may be permanent

Acute Laryngitis

In infants and young children *H influenzae* frequently causes a severe often fatal infection of the larynx usually accompanied by bacteremia

Symptoms and Signs

The disease usually starts abruptly The child may have a nasal discharge or a slight fever for a day or so beforehand and an older

child may complain of a mild sore throat for a few hours preceding the acute illness Then dyspnea appears suddenly and within a few hours grows to an alarming degree Hoarseness and a croupy cough point to laryngeal involvement The temperature by this time has usually reached 102° to 104° F The most characteristic features of the syndrome are pronounced prostration and shock out of all proportion to the amount of local inflammation

On examination the severe respiratory distress is often made evident by cyanosis and restriction of the intercostal suprasternal and infrasternal spaces on inspiration The pharynx is diffusely red and the top of the inflamed epiglottis can be seen Laryngoscopy reveals redness and edema of the true and false vocal cords

Mediastinitis and pericarditis occasionally occur as a result of extension

Laboratory Examinations

A blood culture should be taken in every suspected case since bacteremia is almost always present Nasal and pharyngeal secretions should be typed directly by the capsular swelling method An increase in the leukocytes up to 45 000 per cu mm together with a rise in the proportion of polymorphonuclears is present in nearly every case

Diagnosis

The rapid onset of acute laryngitis in a young child with severe dyspnea and prostration should lead the clinician to suspect *H influenzae* as the cause Culture or direct typing of the laryngeal or pharyngeal secretions or culture of the blood is necessary for certain diagnosis

Differential Diagnosis In simple catarrhal croup and in laryngitis due to infections by other bacteria dyspnea and prostration are not present as they are in *H influenzae* laryngitis Diphtheria can usually be ruled out by the absence of a membrane although smears should always be examined and cultures taken for *C diphtheriae* A retropharyngeal abscess can be felt on digital examination Other conditions which can be ruled out on the basis of the history are pertussis and foreign body in the larynx

Prognosis

If the patients do not receive specific therapy they become rapidly worse and usually die within forty eight hours

Treatment

1 Continuous steam inhalations should be given from the start

2 Sulfadiazine should be given in the same doses as for *H influenzae* meningitis

3 If type B organisms are found specific antiserum may be given also in doses of 100 mg of protein nitrogen or more

4 Although the use of streptomycin in this condition has not been reported the results from this antibiotic should be excellent The dose should be 2 to 3 gm a day divided into six intramuscular injections at four hour intervals

5 Tracheotomy should be done promptly in any case where asphyxia is imminent

H Influenzae Pneumonia

H influenzae was the etiological agent in 0 3 per cent of pneumonias in our patients It is a somewhat more common cause of pneumonia in young children During epidemics of virus influenza the number of cases of pneumonia due to this organism may increase considerably above these nonepidemic figures Pathologically it is a bronchopneumonia and is often bilateral and widespread There are no distinguishing clinical characteristics The onset often is not so abrupt as in pneumococcic pneumonia and the sputum is not typically rusty On the other hand chills and pleural pain may occur as in the pneumococcic variety The fever is irregular and usually high The course is prolonged Empyema and meningitis are frequent complications There is usually a leukocytosis with an increase in the polymorphonuclear cells

Treatment

Therapy with sulfonamides particularly with sulfadiazine has been fairly effective It should be given in the same manner as for pneumococcic pneumonia (see p 120) Durant[5] has successfully treated four patients with streptomycin He used 2 to 6 gm a day intramuscularly and daily instilled 0 05 gm diluted in 5 cc of physiological salt solution into the trachea From our experience we would recommend 2 to 3 gm per day intramuscularly divided into six four hour doses without intratracheal instillations It is best to administer sulfadiazine concomitantly

Other Infections Due to H Influenzae

Endocarditis

H influenzae is one of the infrequent causes of the subacute form of endocarditis Diagnosis and treatment should be carried out in the same way as for endocarditis caused by the nonhemolytic streptococci (p 178) except that streptomycin is used instead of penicillin

Arthritis

When this occurs in conjunction with meningitis it is usually a polyarthritis In cases where meningitis is not present the disease

more commonly affects only a single joint When arthritis is a part of a generalized influenza bacillus infection the treatment need not be modified except that a daily dose of 3 to 4 gm of streptomycin should be administered if it is not already being given If arthritis is present alone similar doses of the antibiotic should be employed

Rarer infections caused by *H influenzae* are conjunctivitis pyelitis and puerperal sepsis

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20 *Klebsiella Pneumoniae (Friedlander's Bacillus)* *Infections*

The *Klebsiella pneumoniae* or Friedlander bacillus is a short plump gram negative rod with rounded ends growing as a single bacillus enclosed in a large capsule or as a pair of bacilli surrounded by a single capsule *It is of historical interest because its discoverer Friedlander* thought it was the cause of most pneumonias and thus precipitated a controversy which raged for many years Numerous observers eventually demonstrated that pneumococci were responsible for the majority of cases of pneumonia and that *Klebsiellae* were only occasionally the etiologic agents We found them to be the causative agents in 0 6 per cent of 2500 cases of primary bacterial pneumonia Today the great practical importance of *Klebsiella pneumoniae* lies in the fact that the clinical picture of the acute pneumonia which it causes is strikingly similar to that seen in pneumococcic infections Since the prognosis and the treatment of the two diseases are not at all alike the clinician must be prepared to differentiate between them

Friedlander bacilli can be typed by agglutination precipitation and capsular swelling methods and are thus differentiated into types A B C D E and a miscellaneous group X

Baehr[1] in studying 198 cases of disease caused by this organism found the majority of infections to be in the gastrointestinal tract (sixty-one cases) the genitourinary tract (fifty cases) and the biliary passages and liver (forty six cases) The lungs and upper respiratory tract were involved in twenty five cases and the female genital organs in six Other sites occasionally affected were the meninges and skin He believes that primary pneumonia is a relatively rare result of infection by the Friedlander organism While the high incidence of gastrointestinal biliary and renal infections is just what would be expected from an organism which is a member of the colon group of bacteria nevertheless it must be remembered that the acute and chronic pulmonary infections caused by the *Klebsiellae* are important because (1) they are the only distinctive diseases which this organism causes and (2) because the acute form is easily mistaken for pneumococcic pneumonia or the chronic form for tuberculosis Furthermore the pneumonias caused by the *Klebsiellae* continue to occur as frequently as in former years whereas because of better sanitation and better surgical diagnosis and treatment infections of the abdominal organs are diminishing in frequency

Klebsiella pneumonia is most frequently observed in persons in the older age groups In 166 collected cases 73 per cent of the patients were over forty years of age The disease has been observed in children although infrequently While alcoholism is mentioned as a predisposing factor we have not observed it any more frequently in such patients than in patients of the same age groups suffering from pneumococcic pneumonia As with the other types of pneumonia the Friedlander variety occurs more frequently during the colder months of the year

Symptoms and Signs

The onset is like that of pneumococcic pneumonia While an antecedent upper respiratory infection may be present the onset of the pneumonia itself is most often sudden Solomon[8] noted a chill at the onset in 63 per cent of his thirty two cases a chest pain in 85 per cent cough in 81 per cent bloody sputum in 75 per cent and vomiting or diarrhea in 28 per cent Malaise headache and prostration are also frequent complaints

Dyspnea and cyanosis are the rule and are often present to a considerable degree The sputum may be gray and tends to be mucoid and tenacious Often it is combined with blood in a homogenous mixture Sometimes frank hemoptysis occurs The temperature may reach a height of 104° or 105° F or it may not go over 102° F even in the sickest patients Herpes simplex is less frequent than in pneumococcic pneumonia Other features frequently observed are delirium distention and jaundice

Examination of the lungs may reveal the typical signs of consolidation over one or more lobes More often the consolidation is characterized by areas in which the breath and voice sounds are diminished or absent interspersed with areas of faint bronchial breathing and pectoriloquy This is what might be expected from the nature of the pathologic process This consists either of separate areas of bronchopneumonia or of a lobar consolidation which is often the result of the confluence of bronchopneumonic patches Any lobe may be involved the upper lobes as frequently as the lower Consolidation of more than one lobe occurs in two thirds of the cases The course may be fulminating with death occurring by the second or third day or in the absence of specific treatment may last a week or two Defervescence is more often by lysis than by crisis

Chronic Pulmonary Infections

A peculiar feature of Friedlander s infection of the lungs which is seldom found in other acute pneumonias is the tendency for the infection to become chronic especially in patients over the age of forty After several days of the acute disease the patient s condition improves

partially but fever continues along with cough expectoration and chest pain Areas of consolidation remain and may extend to other parts of the lungs Bronchiectasis and lung abscesses often develop Solomon[7] sets four weeks as the arbitrary point beyond which a Friedlander pneumonia should be considered chronic The longest duration in any of his cases was three years

A few patients apparently develop the chronic form of the disease insidiously and give a history of cough purulent green yellow or dark red sputum irregular low grade fever anorexia malaise and loss of weight The majority of patients experience the typical onset of klebsiella pneumonia but the disease does not terminate within the expected time The temperature becomes irregular and for the most part lower except during exacerbations The sputum increases in quantity The areas of consolidation may remain the same or increase in extent Signs of lung abscess of bronchiectasis and of pleural fluid appear The fluid may or may not become infected Improvement in patients not treated with sulfonamides or streptomycin may come by slow lysis or may follow surgical drainage of a lung abscess or empyema In some instances fever has persisted for months or years until the *patient was lost sight of Death results less frequently than from the* acute form

Laboratory Examinations

Sputum and Blood In a smear of the sputum large numbers of gram negative bacilli may be seen The large capsules are brought out more clearly when methylene blue stain is used The type can be determined by the capsular swelling method Blood cultures are positive in about 60 per cent of the patients Contrary to the experience in pneumococcic pneumonia the presence of bacteremia does not alter the prognosis materially In the chronic form bacteremia is less frequent occurring in less than 25 per cent of the patients

Leukocyte counts which are low or within the normal range are more common than in the other forms of bacterial pneumonia During the acute phase of the disease the leukocyte count is below 6000 per cu mm *in one fourth of the patients between 6000 and 12 000 in one* third between 12 000 and 20 000 in one fourth and over 20 000 in about one-eighth Complications such as lung abscess empyema or meningitis elevate the leukocyte counts to between 15 000 and 30 000 per cu mm or more In chronic klebsiella pneumonia the leukocyte count is likely to be within or below normal limits except during the acute phases of the illness or in the presence of purulent complications The differential count usually shows a high proportion of neutrophils with an increase in the immature forms although in some instances the relative percentage of monocytes is increased

Roentgen Examinations

Roentgenograms when taken early will usually show an extensive bronchopnuemonia Within a day or two when the areas of consolida tion become confluent the density appears homogeneous At this stage the x ray appearance is similar to that observed in pneumococcic pneumonia except that the distribution of the area of consolidation does not necessarily follow the anatomic markings of the lobes Areas of rarefaction indicating abscess formation and signs of fluid sug gesting empyema may appear later

Complications

Abscess of the lung is the most frequent complication occurring in one fifth of the patients with acute pneumonia and three fifths of those with chronic pulmonary infection The abscesses may be single or multiple and are the result of nonputrid necrosis of areas of lung tissue The sputum becomes mucopurulent and more abundant but is not foul unless the abscess is secondarily infected Continued expectoration of such sputum together with a localized area of large mucous rales may lead the physician to suspect lung abscess although a roent genogram is usually needed to confirm this impression

Sterile pleural effusions occur in one sixth of the patients with acute pneumonia and less often in the chronic form In some instances large amounts of fluid will be present while in others there will be a small encapsulated collection

Empyema results from infection of pleural fluid or from the rupture of an abscess In the latter instance a bronchopleural fistula is some times established leading to pyopneumothorax and frequently re sulting fatally

Other Complications Although bronchiectasis is reported infre quently it is probably common in the chronic form as is fibrosis of the lung with delayed resolution Pericarditis occurs infrequently

Among the complications outside the respiratory system menin gitis is the most frequent Others are endocarditis arthritis and venous thrombosis

Diagnosis

Klebsiellae should be suspected as the cause of any pneumonia with clinical features resembling pneumococcic pneumonia especially if it is accompanied by early severe prostration abscess formation or leukopenia or if the response to sulfonamide therapy is slow or poor Al though a definite diagnosis of Klebsiella pneumonia must depend upon direct typing of sputum by the capsular swelling method or upon culture of sputum blood or other fluids the tentative diagnosis may be made if there is a predominance of encapsulated gram negative bacilli in smears of the sputum Since early streptomycin therapy is

often imperative if the patient is to have a chance to recover treatment may be started on the basis of the stained smear alone

The chronic form most nearly resembles tuberculosis especially if consolidation and abscesses are present in the upper lobes Primary lung abscess bronchiectasis pulmonary neoplasm multiple infarcts and mycotic infections of the lungs are other conditions which may be simulated If Friedlander s bacilli are the cause of the infection they should be demonstrable in repeated sputum examinations or in blood cultures

PROGNOSIS

Before sulfonamides were available three fifths of the patients with the acute form and one-fifth of those with the chronic form died A fatal outcome is more often encountered in patients over forty years of age in patients with extensive pulmonary involvement and in those who develop pulmonary abscesses

TREATMENT

Streptomycin Although the sensitivity of the *Klebsiellae* to streptomycin is variable depending upon the strain tested most of the strains are susceptible to therapeutically achievable concentrations Most of the patients with Friedlander pneumonia who have been treated with this antibiotic have made a satisfactory response The drop in temperature and the clinical improvement are not so dramatic however as those which follow the use of penicillin in pneumococcic pneumonia *The temperature usually falls gradually over the course of three days* to a week and toxicity decreases during the same period of time

An arbitrary dose of 0 5 gm of streptomycin intramuscularly every four hours may be given until the sensitivity of the strain can be tested after which the dose should be increased if necessary in order to obtain a blood concentration four to eight times higher than the sensitivity of the organism Treatment should be continued until the temperature has been normal for at least three days

Sulfonamide In testing the effectiveness of various sulfonamides against klebsiella infections in mice Feinstone[3] found that sulfadiazine was considerably superior to sulfapyridine sulfathiazole and sulfanilamide Schmidt[8] demonstrated that sulfamerazine was nearly as effective as sulfadiazine We have found sulfadiazine to be very effective in patients with Friedlander pneumonia

Sulfadiazine should be given in full doses to patients with either the *acute or chronic form of the disease starting* with 6 gm (90 grains) and followed by 1 gm (15 grains) every four hours Sodium bicarbonate should be administered concomitantly 6 gm (90 grains) with the initial dose and 3 gm (45 grains) with subsequent doses Treatment with this drug should be continued until the patient has been free of

fever for several days If the patient should be hypersensitive the same doses of sulfamerazine may be substituted Since the other sulfonamides are less effective they should not be used unless neither sulfadiazine nor sulfamerazine is available

Combinations of Streptomycin and Sulfonamides Since not all strains of *Klebsiellae* are sensitive to concentrations of streptomycin

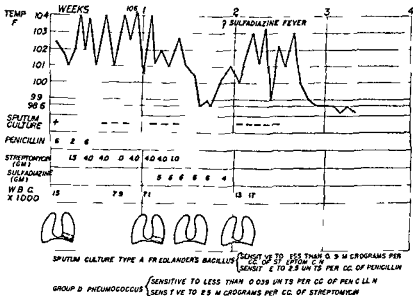


Fig 46 Temperature chart of a patient with pneumonia of the left lower lobe caused by *Klebsiella pneumoniae* Type A treated with streptomycin and sulfadiazine L L a woman aged thirty eight developed substernal pain and cough productive of white frothy sputum one week before admission On admission examination revealed dullness diminished breath sounds and subcrepitant rales in the region of the left lower lobe and a pleuropericardial friction rub Penicillin in wax and oil was started in doses of 600 000 units every twelve hours until a Type A Friedlander's bacillus was recovered from the sputum Streptomycin was then given 0 5 gm every four hours for six days but the temperature continued to spike and the physical findings remained unchanged On the ninth hospital day sulfadiazine was started with prompt drop in temperature for three days On the twelfth day the patient developed nausea vomiting and fever Since the fever was apparently due to the sulfadiazine this drug was discontinued and the temperature again subsided after four days Recovery thereafter was uneventful The higher type pneumococcus which was found in the sputum along with the klebsiella organism may have been contributing to the infection or may have been merely a carrier organism

which can be attained therapeutically and since the severity of the disease demands that treatment be started before the susceptibility of the infecting organism can be determined we feel that it is best to administer both streptomycin and sulfadiazine to all patients

Figure 46 shows a case in which this combination was quite effective

Penicillin Since most strains of *Klebsiellae* are relatively resistant to penicillin in vitro this antibiotic is not recommended for these

infections unless the individual strain responsible for the disease has been tested and found to be sensitive to concentrations of penicillin which can be achieved therapeutically

Figure 47 shows a case in which the organism was sensitive to penicillin and in which penicillin may have contributed to the prompt recovery

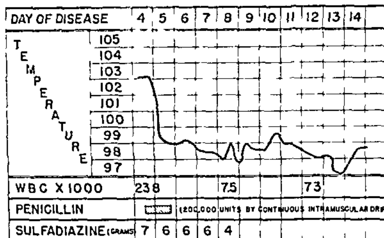


Fig 47 Temperature chart of a patient with pneumonia of the right lower lobe caused by *Klebsiella pneumoniae* Type A treated with sulfadiazine and penicillin

M H a Negro aged twenty five had a head cold with cough three weeks before admission three days before admission chest pain developed and his cough became worse. He was found to have typical signs of consolidation over the left lower lobe *A roentgenogram revealed mottled infiltration in this area indicative of a broncho*pneumonia The leukocyte count was 23,800 per cu mm with 73 per cent segmented polymorphonuclears and 16 per cent band forms Type A *Klebsiella pneumoniae* was obtained in pure culture from the sputum Penicillin inhibited growth of the organism in a concentration of 0 03 units per cc The patient was given 1,200,000 *units of penicillin by continuous intramuscular infusion for the first twenty four* hours of hospitalization and at the same time was started on 6 gm of sulfadiazine followed by 1 gm every four hours. Within fourteen hours after treatment was started the temperature had fallen from 103 to 99 6 F and the patient appeared much less toxic No further penicillin was given but sulfadiazine was continued *for three more days The abnormal physical signs disappeared from the chest by* the tenth day after admission and the patient was discharged the following day The excellent results in this case may have been due to the sulfadiazine alone or to the combination of sulfadiazine and penicillin since this particular strain of *Klebsiella* was moderately sensitive to penicillin

Other Treatment The general measures which should be employed in the management of Friedlander s pneumonia are the same as those outlined for pneumococcic pneumonia (see page 115)

Treatment of Local Complications Abscesses of the lung may clear up on medical treatment which may include streptomycin postural drainage and bronchoscopy If this is not successful surgical

fever for several days If the patient should be hypersensitive the same doses of sulfamerazine may be substituted Since the other sulfonamides are less effective they should not be used unless neither sulfadiazine nor sulfamerazine is available

Combinations of Streptomycin and Sulfonamides Since not all strains of *Klebsiellae* are sensitive to concentrations of streptomycin

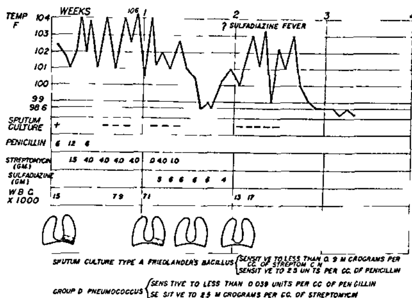


Fig 46 Temperature chart of a patient with pneumonia of the left lower lobe caused by *Klebsiella pneumoniae* Type A treated with streptomycin and sulfadiazine

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Feinstone W H and others The Toxicity Absorption and Chemotherapeutic Activity of 2-Sulfanilamido-pyrimidine (Sulfadiazine) Bull Johns Hopkins Hosp 67 4 7 1940
3 Ferguson J A and Tower A A Pneumonia in Infants Due to Bacillus Mucosus Capsulatus Am J Dis Child 46 59 1933
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6 Schmidt L H Seeler C L and Hughes H B The Chemotherapeutic Activities of Sulfamerazine and Sulfamethazine J Pharmacol & Exper Therap 81 13 1944
7 Solomon S Chronic Friedlander Infections of the Lungs. Report of Seventeen Cases and Observations on Therapy with Sulfapyridine and Sulfanilamide J A M A 115 1527 1940
8 Solomon S Primary Friedlander Pneumonia Report of Thirty Two Cases J A M A 108 937 1937

drainage may be necessary In extremely persistent cases of chronic lung infection with Friedlander bacilli it may be necessary to remove all the foci by lobectomy Empyema may be treated by aspiration of the pus and the instillation of streptomycin in the same way that penicillin is used for pneumococcic empyema (p 125) although the type of pus present in Friedlander empyema makes it more likely that surgical drainage will eventually be needed The dose of streptomycin given by intrapleural injection varies from 5 to 100 mg (in concentrations of 1 to 10 mg per cc of isotonic salt solution) depending upon the sensitivity of the infecting organism

Focal Klebsiella Infections

Meningitis

The meninges are fortunately an infrequent site of infection Ransmeier[5] reported twenty nine patients from the literature and one of his own Only three of the entire group recovered With the introduction of streptomycin the prognosis will undoubtedly improve

Treatment given is streptomycin intrathecally in doses of 05 gm once a day and intramuscularly in doses of 0 5 gm every three hours Sulfadiazine should also be given as in pneumococcic meningitis (see p 130)

Peritonitis

Friedlander infections of the peritoneal cavity occur as a result of extension from the gastrointestinal tract Periappendiceal subphrenic or pelvic abscesses often result In many instances the *Klebsiellae* are mixed with other organisms Large doses of streptomycin are usually necessary in these cases from 0 5 to 0 75 gm every four hours intramuscularly

Urinary tract infections may be caused by *Klebsiellae* alone or in conjunction with other bacteria Obstruction in the urinary tract was a predisposing factor in forty four of Baehr s fifty cases The reader is referred to the section on urinary infections caused by gram negative bacteria (p 126) for the methods of treatment

Other Infections

Cholecystitis and cholangitis are frequently the site of Klebsiella infections Liver abscesses sometimes develop as complications In addition to pneumonias other infections of the respiratory tract may be caused by the *Klebsiellae* such as otitis media mastoiditis and sinusitis

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Glandular Type This type is similar to the *ulceroglandular* except that no primary lesion can be detected

Oculoglandular Type In the oculoglandular type the primary lesion is a conjunctivitis apparently resulting from the transmission



Fig 48 Tularemia primary lesion on hand (From Mackie Hunter and Worth Manual of Tropical Medicine W B Saunders Company)



Fig 49 Nodules along the lymphatics in tularemia

of the bacteria to the eyes by the hands Usually one eye is involved rarely both Itching edema lacrimation photophobia and pain are present in the eyes *followed shortly by enlargement and tenderness* of the preauricular parotid submaxillary and cervical lymph nodes

21 Tularemia and Plague

The *Pasteurellae* are short ovoid gram negative rods or coccobacilli which occur singly and occasionally in chains Two organisms in the group are pathogenic for man *Pasteurella tularensis* which causes tularemia and *Pasteurella pestis* which causes plague Because the etiologic organisms and the diseases which they produce are both much alike we are considering the two diseases in the same chapter Tularemia will be considered in detail while plague will be discussed briefly since it is encountered only rarely in this country at present

Tularemia

Tularemia is a disease caused by *Pasteurella tularensis* It is transmitted by contact with or ingestion of infected animals or birds or by the bites of ticks or insects Among 797 cases collected from the literature handling or eating wild rabbits was responsible for the infection in 89 per cent of the patients Bites by deerflies or ticks or crushing ticks in the fingers accounted for 6 per cent while the remainder were the result of bites or scratches from or direct contact with a variety of animals including squirrels opossums and cats and rarely game birds Laboratory infections account for an occasional case and epidemics have occurred from infected drinking water More rarely the disease is contracted by someone while dressing the ulcer of a tularemic patient

Pathology

The disease is classified into four clinical types ulceroglandular glandular oculoglandular and cryptogenic

Ulceroglandular Type In the ulceroglandular type a small red papule appears at the point where the bacteria enter the skin at or soon after the onset of the general symptoms The papule rapidly becomes pustular and sloughs away to leave a punched out ulcer with raised edges which heals slowly (Fig 48) The regional lymph nodes enlarge and become tender Sometimes as a result of secondary infection red streaks extend upward along the lymphatics In some patients series of nodules appear along the course of the lymphatics (Fig 49) In about half of the patients the lymph nodes or the nodules along the lymphatic vessels suppurate The lymph nodes may remain enlarged for weeks or months Sometimes they shrink to normal size only to swell again for a variable period of time

tularemia than in any other disease A rise in agglutinins may begin as early as the eighth day of illness and usually occurs some time during the second week although it may not take place until the third or rarely the fourth week By that time the titer is at its maximum which may be anywhere from 1 320 to 1 10 240 or higher It falls gradually over the course of years often being still present ten or twelve years after the disease In the absence of previous tularemia a titer of at least 1 160 or preferably rising titers should make the diagnosis certain There is one exception serums of patients with brucellosis and tularemia sometimes cross agglutinate Accordingly serums should always be tested against both organisms whenever either disease is suspected The titer obtained with the organisms causing the disease will be higher than that obtained against the heterologous organism

Earlier diagnosis can be made according to Foshay [2] with an *intradermal test* using 0 05 cc of a specially prepared suspension of the killed organisms A positive reaction shows a zone of erythema and edema 1 cm or more in diameter forty-eight hours after the injection

In contrast to many other diseases cultures of the blood of the primary lesion and affected lymph nodes or body fluids of a tularemic patient seldom yield the organism although inoculation of guinea pigs with these materials is likely to be successful Sputum inoculated into mice will often yield the organisms In view of the fact that a potent therapeutic agent streptomycin is now available early diagnosis is imperative in severely ill patients In such instances the diagnosis should be made if possible by animal inoculation before agglutinins appear

COMPLICATIONS

Pulmonary Complications Pneumonia occurred in 22 per cent of tularemic patients studied roentgenologically by Blackford [1] It is found in more than half of the patients with the cryptogenic form of the disease In most cases the bacteria reach the lungs from the primary focus through the blood stream In rare instances tularemia may resemble plague in that the organisms are inhaled and cause pneumonia from the start The pulmonary lesions consist in a confluent bronchopneumonia involving one or more lobes with focal areas of necrosis which often cause the formation of single or multiple abscesses

The onset of the pneumonia is usually gradual and may take place at any time within the first two weeks of the tularemic infection Cough is almost invariably present Chest pain and tenacious mucopurulent sputum are each present in about half of the patients Patches of consolidation and in extensive cases consolidation of entire lobes may be detected by physical examination and x ray Fever is generally high for from two to four weeks and declines by lysis The areas of

The conjunctivae are swollen and bright red with scattered small yellow nodules on the palpebral and occasionally also on the bulbar conjunctivae Later these break down to form ulcers Sometimes there is a gray translucent exudate over the conjunctivae The discharge becomes mucopurulent and then gradually decreases, along with the swelling of the conjunctivae after about three to five weeks Subcutaneous nodules may be present between the eyes and regional lymph nodes The ophthalmic lesions usually heal without permanent impairment of vision although dacrocystitis corneal ulcers and even blindness are occasional sequels

Cryptogenic Type In the cryptogenic (sometimes called typhoidal) type the point of entry of the organisms cannot be recognized and the symptoms are entirely systemic

Symptoms and Signs

The incubation period is from one to four days in 80 per cent of the patients and one week or less in 95 per cent The onset is usually sudden with chills or chilly sensations fever sweating malaise general aching and sometimes nausea and vomiting In the milder cases there may be nothing more than slight malaise and a low grade fever and rarely a patient experiences no constitutional symptoms at all

The systemic manifestations common to all types are

1 The usual symptoms of a bacterial infection chills fever sweating malaise prostration arthralgia and myalgia The temperature is usually irregularly remittent occasionally intermittent or in some severe cases high and continuous There may be periods of low grade or no fever followed by high fever Fever usually lasts two to four weeks but complications may cause it to persist several weeks longer

2 Transient bacteremia probably occurs in the first few days in all patients In fatal cases the bacteria usually reenter the blood a few days before death and remain there

3 General lymphadenopathy occurs in an occasional patient

4 Cutaneous eruptions appear in about 10 to 20 per cent of patients They are seen most often on the arms neck and upper part of the trunk and take no distinctive form The lesions are most frequently papular but may be macular vesicular or pustular The typical lesions of erythema nodosum appear occasionally

Laboratory Examinations

The *leukocyte count* may remain within normal limits or may be slightly elevated Rarely it is increased to between 20 000 and 30 000 per cu mm

The *agglutination test* is perhaps more valuable for diagnosis in

PROGNOSIS

As far as recovery from the disease is concerned the prognosis is good Before streptomycin was available 5 to 10 per cent of all patients died Since this antibiotic has come into general use the outlook has been even more favorable As in most infectious diseases the heaviest toll is exacted from the very young and the older age groups Death seldom occurs in patients between the ages of ten and thirty years When certain factors are present the prognosis is poorer Among patients with pneumonia treated before the advent of streptomycin for instance about 30 per cent died since this complication is more frequent when there is general dissemination of the bacteria The fatality was likewise greater in patients with the cryptogenic form of the disease About 20 per cent of these patients died contrasted with 5 per cent of those suffering from one of the other types

TREATMENT

Streptomycin Relatively low concentrations of streptomycin inhibit the growth of *P tularensis* in the test tube and exert a curative effect upon the experimental disease in rodents[3] Enough patients with tularemia have now been treated to demonstrate that streptomycin is without doubt the most effective therapeutic agent available for the disease in humans During the first month or two of the disease the patients almost invariably respond to streptomycin therapy with a dramatic drop in temperature to normal or nearly normal levels When patients are treated later than this the response is variable possibly owing to the presence of circumscribed foci of infection which are not readily accessible to the streptomycin Howe[4] and Hunt[5] have shown that patients with the cryptogenic form of the disease and those with pneumonia respond as do patients with the ulceroglandular type

Relatively small doses of streptomycin are sufficient to overcome the disease From 0 1 to 0 2 gm should be injected intramuscularly every four hours (0 6 to 1 2 gm per day) If the patient has a high continuous fever or extensive pneumonia or if he is extremely toxic larger doses such as 2 4 to 3 6 gm a day may be needed although Hunt[5] obtained excellent results in severely ill patients with pneumonia with doses of 1 6 gm a day or less Administration should be continued until the temperature has fallen and has remained within normal or nearly normal limits for three or four days If relapse occurs after streptomycin therapy has been discontinued a second course of double the previous dose should be given

Primary Ulcers Primary ulcers may be soaked in a saturated solution of magnesium sulfate or after preliminary cleaning covered with a sterile dry dressing and let alone They should not be incised

consolidation resolve slowly When definite cavitation occurs the course is longer and the prognosis worse Before streptomycin was available death occurred in about 30 per cent of the patients with pneumonia and in about two thirds of those with abscess formation

Pleural effusions are observed in 5 to 15 per cent of tularemic patients sometimes alone and sometimes in conjunction with pneumonia Although large quantities of fluid may be present and may continue to accumulate in spite of repeated chest taps the condition eventually clears up except in those patients who die of the underlying pneumonia

Acute bronchitis is observed in about 20 per cent of patients It is of little significance except that it usually leaves behind evidences of peribronchial fibrosis

Suppuration of the regional lymph nodes occurs in about 30 per cent of patients Aside from the fact that the disease lasts longer in these patients this phenomenon is relatively unimportant

Other Complications Peritonitis hepatitis perisplenitis meningitis encephalitis pericarditis and osteomyelitis are among the less frequent complications Since they are evidences of extensive spread of the bacteria they are accompanied by considerable toxicity and often end fatally

Diagnosis

When the patient has a manual ulcer or conjunctivitis together with regional lymphadenopathy and a history of handling rabbits or other wild animals the diagnosis of tularemia is very probable But in patients who have an ulcer in less characteristic parts of the body or in those with no local lesion and only general symptoms of a severe infection this disease is likely to be overlooked When tularemia is suspected regardless of its form the diagnosis should be substantiated by *agglutination reactions intradermal tests and if necessary* inoculation of animals with sputum blood body fluids or material from ulcers

Differential Diagnosis This depends upon the type of tularemia present The local lesion may be confused with an ulcer caused by the pyogenic cocci with syphilis or anthrax The glandular form is similar to plague *Nodules along the course of the lymphatic vessels may be* found in two other diseases sporotrichosis and sarcoidosis A careful history bacteriologic studies of the lesion serologic and intradermal tests will distinguish between the diseases mentioned The cryptogenic form of the disease may simulate typhoid and undulant fevers plague miliary tuberculosis or the pneumonias caused by other agents Here reliance must be placed upon laboratory procedures to make the differentiation

or no enlargement of superficial lymph nodes The course is fulminating and ends in death within a few days

Primary Pneumonic Type This form occurs when the bacteria are inhaled as a result of contact with a patient with plague pneumonia or sometimes after the skinning of an infected animal It occurs occasionally as a winter epidemic in some parts of the world The incubation period is one to two days The onset is abrupt with a chill or chilly sensations followed by blood tinged mucoid or thin bright red sputum It was considered to be invariably fatal before sulfonamides were used

Complications

Pneumonia is a frequent complication in cases where it is not primary It is either a patchy or a confluent bronchopneumonia often characterized by frankly bloody sputum Pleurisy is often present also

Meningitis and encephalitis are uncommon complications which are almost invariably fatal when they occur Among 203 patients with plague reported by Landsborough [7] there were eight cases of meningitis all of which were fatal in spite of sulfathiazole treatment Meyer[8] has reported a case of chronic plague meningitis and has reviewed the literature on the subject

Meningismus delirium and convulsions are not uncommon in plague in the absence of meningitis On the other hand if nuchal rigidity abnormal neurological signs or disturbances of the sensorium are present a *lumbar puncture should always be performed* In meningitis it will reveal the characteristic features of a bacterial meningitis cloudy fluid which is under increased pressure and contains a higher number of polymorphonuclears elevated protein content and decreased or absent dextrose The color of the fluid is often a distinctive canary yellow

Laboratory Examinations

The *organisms can sometimes be obtained in stained smears of* material from lymph nodes sputum blood and cerebrospinal fluid They can also be demonstrated on culture and by guinea pig inoculation The optimal temperature for the growth of the cultures is around 30 C Leukocytosis is present and the white cell count may reach 40 000 per cu mm

Diagnosis

The presence of fever toxemia and leukocytosis in persons who might have come in contact with infected rats or ground squirrels is highly suspicious of plague In the United States this possibility arises chiefly in the western states The appearance of buboes or of signs of pneumonia accompanied by bloody sputum makes the diagnosis more

as incision may produce chills and fever—evidences of the pouring of bacteria into the circulation when the natural barriers are destroyed

Eye Lesions These are best treated by washing the conjunctival sacs at frequent intervals with a warm saturated solution of boric acid and applying during the remainder of the time hot compresses of a saturated solution of magnesium sulfate diluted with an equal amount of water

Lymph Nodes and Lymphatics The affected lymph nodes and all others likely to be involved should be inspected and palpated each day Those which show fluctuation should be incised sufficiently to permit adequate drainage Painful nodes should be treated with compresses of warm saturated solution of magnesium sulfate

Nodules along the lymphatics seldom need any attention unless they suppurate in which event they should be incised and drained

Other Treatment Symptomatic and supportive measures should be carried out as in other infectious diseases (p 15) Attendants should protect themselves against infection from open lesions even though the chances of spread from man to man are slight

Sulfonamides and penicillin are of no value in tularemia The specific antiserum developed by Foshay[2] is so much less effective than streptomycin that it will undoubtedly pass into disuse

Plague

Plague is a disease caused by *Pasteurella pestis* and transmitted to man by the bites of insects carried by rats or wild rodents and from man to man by the inhalation of infected droplets

Symptoms and Signs

Bubonic Type After an incubation period of two to ten days there is an abrupt onset of fever usually with a chill or chilly sensations and accompanied by malaise weakness backache and headache A local lesion at the site of the bite may be seen but is usually not present The lymph nodes (buboes) are enlarged and tender especially in the area drained by the local lesion Vomiting diarrhea convulsions and delirium may occur The temperature is irregular reaching peaks of 103° to 104 F in the average case

When fully developed the buboes are hard and tender and may be as large as an egg These typical lesions are present in about 75 per cent of cases Suppuration is common in patients who live long enough

Mild cases (often called *Pestis minor*) occur in which there is little or no toxemia and fever and only one small or moderate sized bubo

Primary Septicemic Type This is a variant of the bubonic type in which the insect bite is followed quickly by a bacteremia with little

Among bacteremic patients the differences were even more striking, the fatality rates being 36, 53 and 92 per cent respectively. Huang[6] reported that none of his patients with bubonic plague died when treatment with sulfadiazine was started before the third day of the disease. Sulfonamides are less effective in the primary septicemic and primary pneumonic forms of the disease, although a case of the latter has been reported in which the patient recovered after sulfadiazine therapy.[9]

Streptomycin. *P. pestis* is one of the organisms which are quite sensitive to streptomycin in vitro. Wayson[11] showed that recovery from experimentally induced plague infection will occur in the majority of mice and guinea pigs treated with streptomycin. The results were no better than, if as good as, those obtained with sulfadiazine. If streptomycin is used in human patients, it is probable that large amounts would be needed, such as 3 to 4 gm. a day, divided into six equal doses and given intramuscularly at four hour intervals.

Serum. Antiplague serum made from horses has been extensively *used in the past. Although the results obtained have been fairly good*, serum is not so effective as sulfonamides in lowering the fatality rate and has been *displaced by other agents*.

Local Treatment. Hot, wet dressings should be applied to the buboes. When frank fluctuation occurs, but not before, they should be incised.

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likely. The organism should always be sought for in any suspicious case by culture and guinea pig inoculation.

Differential Diagnosis. The bubonic form in its early stages and the primary septicemic form can be mistaken for any of the generalized fevers, particularly typhoid fever, typhus fever, malaria and other tropical fevers. Tularemia has forms which correspond to those of bubonic plague and therefore mimics it at all points. The pneumonic form of plague may be similar to pneumococcic and the other bacterial pneumonias. Lymphopathia venereum and chancroid will also produce swollen inguinal nodes. The buboes of plague develop more rapidly, are more painful and are accompanied by far greater constitutional symptoms.

Prognosis

Before the advent of the sulfonamides and of streptomycin the fatality rate for bubonic plague averaged 50 per cent or more, while patients with primary pneumonic and primary septicemic plague only rarely recovered.

Prevention

A vaccine containing 2000 million bacteria per cc. should be given in two subcutaneous injections of 0.5 and 1.0 cc., respectively, a week or ten days apart. A booster injection of 1.0 cc. is advisable at a later time if exposure is imminent. Although prevention is not absolute, immunization reduces the fatality rate to about one-sixth of the rate in nonimmunized persons.

Treatment

Sulfonamides. Sulfadiazine and, to a lesser extent, sulfathiazole are the most valuable therapeutic agents available at the present time. Large doses of sulfadiazine should be given, 6 gm. (90 grains) initially and 1.5 gm. ($22\frac{1}{2}$ grains) every four hours, accompanied by 6 gm. (90 grains) of sodium bicarbonate initially and 3 gm. (45 grains) with each succeeding dose. Intravenous injections of sodium sulfadiazine may be given in the same initial dose, followed by subcutaneous injections containing 1.5 gm. ($22\frac{1}{2}$ grains) of sodium sulfadiazine every eight hours, or more often if necessary to maintain a blood sulfadiazine concentration of 15 to 20 mg. per 100 cc. Proper precautions should be taken against the development of renal calculi and other complications of sulfonamide therapy (see p. 62). Sulfonamide treatment should be continued for ten to fifteen days after the temperature has reached normal.

The results with sulfadiazine in bubonic plague have been good. Wagle[10] observed a fatality rate of 22 per cent in patients treated with this drug, compared with 34 per cent among those who received sulfathiazole and 58 per cent among patients who received neither drug

surrounding the lesion often extends over a wide area of the body When the lesion is on the neck the edema may extend into the mouth pharynx or larynx often with grave consequences The local lesion is seldom actually painful although itching burning and throbbing sensations and a feeling of fullness are present The regional lymph nodes are swollen painful and tender

After the vesicles rupture and begin to dry the edema begins to subside Improvement is usually rapid from that time on Tenderness of the regional lymph nodes disappears within a few days

The general symptoms associated with the cutaneous lesion may be surprisingly mild although ordinarily there are malaise headache

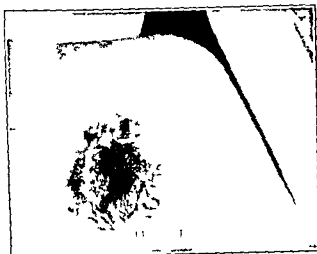


Fig 50 Typical eschar of anthrax on the eighth day of the disease The surrounding vesicles have ruptured and dried (From Ellingson Kadull Bookwalter and Howe *J.A.M.A* *131* *110* *1946*)

joint pains and a slight or moderate amount of fever Ellingson[4] found general symptoms in five of his twenty five patients

Gastrointestinal Type When the bacteria are *ingested* severe gastrointestinal symptoms appear abdominal pain vomiting and diarrhea The stools and vomitus are either bloody or have the typical coffee grounds appearance of changed blood The temperature is elevated except when peripheral collapse supervenes a catastrophe characterized by a fall in the temperature a rise in the pulse rate and frequently death within a few hours

Pulmonary Type Breathing dust from infected wool hides hair or other material may result in inhalation of anthrax bacilli followed by bronchitis and patchy bronchopneumonia Although the onset may be gradual it is usually abrupt with a chill or chilly sensations fever

22 Anthrax

Bacillus anthracis is a large encapsulated gram positive rod with squared ends It is of historical importance because it was one of the first micro-organisms to be recognized and studied and of clinical significance because it is responsible for a serious occupational disease called anthrax Anthrax bacilli are spore formers and are extremely persistent in warm or moist contaminated soils whence they infect animals and produce disease in the skin the pharynx or in the intestines Man becomes infected from handling diseased animals or by contact with infected hides skins wool hair or bristles Anthrax is not a common disease Only forty nine cases were reported in the United States for the year 1944

The anthrax bacillus tends to attack three different areas in man the skin the lungs or the intestines In the cutaneous variety (which is the most common) there is exudation of blood and serum and coagulation necrosis in the subcutaneous tissues usually in a single location In the intestinal type hemorrhagic areas are found in the small intestine or cecum In pulmonary anthrax patchy areas of hemorrhagic consolidation are present in the lungs along with hemorrhagic exudate covering the walls of the bronchi Regional lymph nodes are involved in all types

SYMPTOMS AND SIGNS

Cutaneous Type Among 937 cases of anthrax of the skin reported by Legge[6] the frequency of involvement of the different sites was as follows head and face 45 per cent neck 31 per cent upper extremity 20 per cent lower extremity and trunk each 2 per cent The incubation period varies from one half to five days The local lesion has been vividly and succinctly described by Lebowich[3] as follows It began as a single small pale red papule on an exposed surface The lesion rapidly enlarged during the next forty-eight to seventy two hours to reach a diameter of from 1 0 to 2 5 cm with the development of a central necrotic brownish black eschar surrounded by an adjacent ring of multiple raised monolocular pink vesicles and a diffuse and disproportionate zone of soft doughy pink to red swelling

On the fifth or sixth day of the evolution of the lesion the eschar extends to include the crusting vesicles around the periphery (Fig 50) The eventual size of the pustule may vary anywhere up to several cubic centimeters in diameter In the majority of cases there is only one cutaneous lesion occasionally there are two or more The edema

surrounding the lesion often extends over a wide area of the body When the lesion is on the neck the edema may extend into the mouth pharynx or larynx often with grave consequences The local lesion is seldom actually painful although itching burning and throbbing sensations and a feeling of fullness are present The regional lymph nodes are swollen painful and tender

After the vesicles rupture and begin to dry the edema begins to subside Improvement is usually rapid from that time on Tenderness of the regional lymph nodes disappears within a few days

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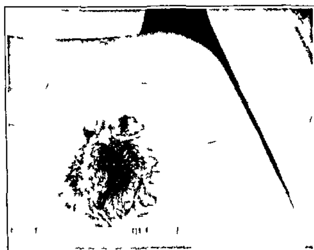


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and cough with the expectoration of thin or foamy bloody sputum Physical examination will reveal bronchitis and bronchopneumonia Dyspnea and cyanosis are pronounced Death often occurs in less than a week

Complications

These are not common Gangrene may occasionally supervene upon the local lesion and rarely in the healing of the cutaneous type scar formation may be so great as to require plastic surgery Meningitis and meningo encephalitis are rare complications characterized by bloody cerebrospinal fluid which contains anthrax bacilli They are manifestations of overwhelming disease such as may be encountered occasionally in patients with the pulmonary or intestinal form

Laboratory Examinations

It is surprising that in such a severe infection leukocytosis is not more pronounced In many cases the white blood cell count is within normal limits In others it may be increased moderately although it is seldom above 20 000 per cu mm The percentage of polymorphonuclear cells is increased

Ellingson[1] cultured the organisms from the blood of three out of twenty five patients with cutaneous anthrax Positive blood cultures are more frequent than this in patients with the cutaneous form just before death and in patients who have the disease in the intestines lungs or meninges

B anthracis can often be seen in stained smears and can be cultured readily from the cutaneous lesion especially from the clear fluid which is aspirated from the vesicles If necessary the material may be inoculated into guinea pigs or mice When the pulmonary or intestinal form is suspected the sputum vomitus or stools should be cultured

Diagnosis

If the clinician remains alert to the suspicion of anthrax the history of exposure and the appearance of the lesion usually make the diagnosis of the cutaneous form easy Lack of pain and the absence of pus are characteristic features Provisional bacteriologic diagnosis can frequently be made by microscopic demonstration of the large bacilli which occur singly or in jointed pairs Further confirmation can be obtained within twenty four to thirty six hours by culture of the vesicular fluid

When the lungs gastrointestinal tract or meninges are involved there is nothing in the clinical picture to distinguish the disease from infections by other bacteria Anthrax may be suspected from a history of exposure although exact diagnosis must rely upon bacteriological identification

lesion diminishes within a few hours and that the control of this edema is the most reliable criterion for determining whether further serum is necessary

In view of the excellent results obtained with the sulfonamides and particularly with penicillin serum will probably be discarded If it is employed proper precautions should be taken before administration to minimize the number and extent of serum reactions (see p 33)

Neoarsphenamine Some effect upon the disease has been obtained from the use of this drug although the results of its employment are difficult to evaluate since it has usually been administered in combination with other agents Hodgson[3, 4] for instance reported six deaths among fifty two patients treated with serum alone and no fatalities among fifty five patients who received serum plus neoarsphenamine He recommends 0 3 gm of neoarsphenamine on the first day of treatment 0 15 gm on the third day and in severely ill patients another 0 3 gm on the fifth day Penicillin and sulfonamides have now caused this drug to be outmoded

Sulfonamides Several different sulfonamides have given beneficial results in anthrax Gold[2] treated forty two patients with sulfapyridine sulfathiazole and sulfadiazine with satisfactory response in thirty nine The other three required serum in addition before recovery ensued He believes that sulfathiazole is the drug of choice Response to sulfonamides does not seem to be so prompt as that following serum administration Since the response to penicillin is superior the sulfonamides will apparently no longer be necessary There is no evidence that combinations of penicillin and sulfonamides give better results than penicillin alone

Other Measures Among the other therapeutic measures which have been tried are x ray therapy and immunotransfusion The newer agents now available will undoubtedly render unnecessary any further trial of these doubtful measures

Patients with internal forms of the disease may need fluids and plasma to combat shock When pulmonary involvement is present oxygen should be used for cyanosis or other evidences of respiratory embarrassment (see p 17)

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1 Ellingson H V Kadull P J Bookwalter H L and Howe C Cutaneous Anthrax Report of Twenty Five Cases J A M A *131* 1105 1946
2 Gold H Anth[illegible] A Review of Sixty Cases with a Report on the Therapeutic Use of [illegible] [illegible]de Compounds Arch Int Med *70* [illegible]8 194[illegible]
3 Hodgson [illegible] [illegible]s Anthrax Lancet *1* 811 1941
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Differential Diagnosis The local lesion may be simulated by an abscess or carbuncle with a central gangrenous area resulting from treatment with escharotics by a gangrenous extragenital chancre and by accidental vaccinia History and bacteriologic examination will clear up the diagnosis in these cases

PROGNOSIS

Before modern methods of treatment were available about one fourth of the patients with cutaneous anthrax died The internal forms of the disease were much more virulent most of the cases of the gastro-intestinal type and practically all of the pulmonary type being fatal

TREATMENT

Penicillin In in vitro experiments *B anthracis* has been found to be moderately sensitive to penicillin The use of this antibiotic has been reported in only a few patients but the reports have all been favorable In cutaneous anthrax the temperature usually drops rapidly after penicillin therapy is started more rapidly in fact than after any other therapeutic agent Frequently the temperature is normal within twenty four hours after the first dose Murphy[7] treated three patients and observed prompt disappearance of the erythema and induration and rapid drying and disappearance of the lesion Ellingson[8] reported excellent results in all his twenty five patients treated with penicillin The bacilli could no longer be cultured from the local lesion in twenty three of the cases within forty-eight hours after the beginning of treatment

Doses of 15 000 to 25 000 units intramuscularly every three hours seem to be satisfactory for the average case of cutaneous anthrax When the patient is very toxic when the bacilli are cultured from the blood or when internal forms of the disease are present larger doses up to 1 000 000 units a day will be necessary These larger doses may be given by intermittent intramuscular injections or by continuous intramuscular or intravenous infusion

The results of treatment with penicillin are so much more satisfactory than those obtained with any of the other therapeutic agents that this antibiotic is recommended for routine use in all cases Therapy should be continued for at least five days or until the temperature is normal *the systemic symptoms have disappeared the edema has* started to subside and the lesions are beginning to dry

Specific antiserum has been used extensively in the past with excellent results In large series of patients with cutaneous anthrax the fatality rate was 5 per cent or less Serum is administered in doses of 200 to 500 cc every eight to twenty four hours until the infection is under control Patients who are very toxic or who have bacteremia are given the larger amounts Gold[9] states that the edema around the local

lesion diminishes within a few hours and that the control of this edema is the most reliable criterion for determining whether further serum is necessary

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Part IV

BACTERIAL DISEASES IN WHICH EXOTOXINS ARE A MAJOR FACTOR

23 Diphtheria

BY

LEWIS K. SWEET

Diphtheria or membranous croup is a specific disease caused by the *Corynebacterium diphtheriae* and characterized by both local and systemic lesions. All lesions are the result of the action of a toxin produced by the bacillus and of the tissue response to the toxin.

Etiology

The *C. diphtheriae* or the Klebs-Loeffler bacillus is a rod-shaped, nonmotile organism that varies considerably in size and shape. Usually it is slender and slightly curved, though it may be straight. When stained by Gram's method it is gram-positive, and when stained by Ponder's or other differential stains it shows granular polar bodies at one or both ends, often with granulation between.

The diphtheria bacillus, when it grows either in the body or on artificial culture medium, excretes a soluble substance that is extremely poisonous to protoplasm. This substance is the toxin of diphtheria. Strains of bacilli differ in their ability to produce toxin. Those which produce potent toxin are regarded as virulent, while those producing little or no toxin are avirulent.

C. diphtheriae can be typed by cultural and fermentation reactions into *gravis*, *intermedius* and *mitis* types,[1] with a few atypical strains. Within each of these cultural types are several serological types. In general the cultural types differ considerably in their virulence and pathogenicity, the *gravis* type producing toxin both more rapidly and in much greater abundance than the *mitis* or *intermedius* types.[14, 27] Also the *gravis* type is much more prone to tissue invasion and is more resistant to the bactericidal power of whole blood than are the other types. Specifically, however, individual strains of any type may be of extremely high or low virulence, so that *gravis* strains may be completely avirulent, while *mitis* strains may be so virulent as to produce malignant diphtheria. The *gravis* strains have been largely

responsible for the extremely malignant and fatal epidemics of recent years in Europe and when recovered in such epidemics almost invariably are highly virulent[14] Conversely organisms of the *gravis* type have been reported rarely in America and frequently are non virulent[5] There is no demonstrable difference in the toxin excreted by the various types of *C diphtheriae* and an antitoxin that is potent against one type is potent against all[4]

Pathology

The pathologic lesions of diphtheria are both local and general *The local lesion at whatever site the virulent organisms are implanted* in a nonimmune host is caused by an outpouring of toxin from the organisms which grow in the cellular detritus on the mucous membrane or in the wound This toxin causes a local tissue necrosis which in turn promotes further growth of the bacteria further toxin production and greater extension of the local lesion

As the epithelial cells become necrotic there is a marked outpouring of fibrinous exudate from the blood stream into the subjacent tissues This is accompanied by some leukocytic infiltration and small hemorrhages This exudation forms a membrane called the false membrane On section it is found to be dense and composed of layers of fibrin with an admixture of leukocytes red blood cells and bacteria Secondary invaders such as streptococci are often seen in the congested or swollen subjacent tissues

The systemic lesions are due to the effects of toxin which is transported from the local lesion through either the lymphatics or the blood When there is a severe degree of toxemia there is some necrosis of almost all tissues of the body The effects of this necrosis are much more pronounced in the more highly developed structures such as the myocardium and the central nervous system with less damage to the liver the kidneys the reticulo endothelial system and the other viscera In the liver this results in disturbance of glycogen metabolism and secondarily of generalized carbohydrate metabolism In the kidneys *there may be serious nephritis though there is no clinical type of* nephritis that is characteristic of diphtheria The primary lesion in the heart muscle is a toxic necrosis with cloudy swelling loss of muscle striation and hyaline degeneration with a secondary infiltration of inflammation and fibrosis that lead to repair

The toxin attacks the central nervous system either through the *myoneural junction up the perineural lymphatics or along the nerves* Since there is a much greater concentration of toxin in the pharynx and upper air passages there is frequently an early involvement of the cranial nerves especially those supplying the palate and pharynx and less commonly the orbital nerves There is a widespread usually late involvement of the nervous system in toxic patients who receive

treatment late or in inadequate amounts There is fatty degeneration in the myelin sheaths of involved peripheral nerves but central lesions are inconstant or absent

Symptoms and Signs

Incubation Period Diphtheria usually becomes manifest two to four days after exposure to it but the incubation period may vary from one to seven days Usually there are no constitutional symptoms until there is considerable local involvement

Local Symptoms and Signs Diphtheritic lesions are found commonly on the mucous membrane of the tonsils palate pharynx and nasopharynx with less frequent localization in the nose larynx and trachea Rarely there is extension to the bronchi bronchioles and even to the pulmonary alveoli In rare instances there is primary involvement of the skin through superficial wounds or of the mucous membrane of the vagina or eye

The early local symptoms of pharyngeal involvement usually start with irritation and pain in the throat the pain being aggravated on swallowing Occasionally however there is no pain even in well developed diphtheria The earliest signs are intense injection and hyperemia of the site involved There may be one or many white or cream-colored lesions which grow rapidly and soon become confluent The false membrane so formed is at first white or creamy in color but as it thickens it becomes gray or gray green If there is hemorrhage into the lesion it darkens until it becomes almost black As the lesion advances there usually is greater soreness of the throat and the membrane increases not only in size but in thickness even to a depth of 4 or 5 mm Edema may be present at times to a rather extreme degree though it usually is absent In some instances considerable force may be required to separate the membrane from the underlying tissues When the false membrane is removed there are small bleeding areas over the denuded surface

If there is local extension into the nasopharynx and nose the nasal airways are clogged and a serosanguineous discharge appears at the nares The discharge is often unilateral Visualization of the nasal mucosa shows the same type of grayish white membrane over the surface If there is extension downward the larynx trachea and bronchi may be involved With involvement of the larynx there is hoarseness with a harsh cough followed by aphonia On direct examination a false membrane is seen over the vocal cords and at times over the entire glottis The membrane is not so thick or dark as that found in the pharynx or fauces and it can be detached with greater ease As the laryngeal involvement progresses there is moderate to marked edema which together with the membrane causes obstruction of the normal airway

responsible for the extremely malignant and fatal epidemics of recent years in Europe and when recovered in such epidemics almost invariably are highly virulent[14] Conversely organisms of the *gravis* type have been reported rarely in America and frequently are non virulent[5] There is no demonstrable difference in the toxin excreted by the various types of *C diphtheriae* and an antitoxin that is potent against one type is potent against all[4]

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The toxin attacks the central nervous system either through the myoneural junction up the perineural lymphatics or along the nerves Since there is a much greater concentration of toxin in the pharynx and upper air passages there is frequently an early involvement of the cranial nerves especially those supplying the palate and pharynx and less commonly the orbital nerves There is a widespread usually late involvement of the nervous system in toxic patients who receive

collar around the patient's neck. The neck may be so broad that there is a gradual tapering out from the head to the shoulder girdle. This is the so-called "bull neck."





Fig. 51. Types of lesions observed in cutaneous diphtheria. (Army Institute of Pathology Nos. 639 and 633.)

Cutaneous diphtheria was seen among troops in the tropical and subtropical regions with considerable frequency during World War II. The primary lesion is a small vesicle surrounded by a large area of erythema. The lesion rapidly undercuts and becomes an ulcer with an extremely tenacious fibrinous membrane. It then spreads and en

The evidences of laryngeal involvement are quite distinct as a rule The voice is hoarse or the patient may be completely aphonic If there is partial occlusion of the glottis the respirations assume a metallic or tubular quality There is a hoarse deep seated cough that can be explained no more characteristically than by calling it croupy As the glottic opening is reduced the patient becomes restless and anxious and dyspnea appears There is retraction of the intercostal supra sternal and infrasternal spaces the accessory muscles of respiration are brought into use and cyanosis becomes evident The pulse remains strong at first (unless there is an extensive nasopharyngeal diphtheria with pronounced toxemia) but as the dyspnea increases and fatigue commences the pulse becomes more rapid of lesser volume and irregular If there is an associated toxic nasopharyngeal diphtheria heart failure comes sooner and more rapidly As the patient s strength fails the retraction of the chest becomes less and the breathing may be less stertorous and apparently easier The face however remains cyanosed and congested and the pulse continues to fail Restlessness recedes and cyanosis deepens as a fatal termination approaches

There are few symptoms from tracheal involvement that are not masked by the usually concomitant laryngeal diphtheria As the bronchi bronchioles and alveoli are involved however there develops a more difficult respiratory exchange with a rapid grunting type of respiration rales over the involved areas and at times all the signs and symptoms of a pneumonia

While laryngeal and tracheobronchial diphtheria often are secondary to or are accompanied by pharyngeal or faucial diphtheria it is of the utmost importance to remember that involvement of the larynx or trachea may be present when there is absolutely no membrane in the visible oropharynx If the history and clinical picture suggest diphtheria of if the diagnosis of diphtheria cannot be excluded the condition should be appraised by direct laryngoscopic or bronchoscopic examination Direct cultures should be made at this time

Local or regional involvement in diphtheria is accompanied by involvement of the cervical lymph nodes in many patients The cause of this involvement may be either the diphtheria toxin *C diphtheriae* itself in some instances of *gravis* infection or a secondary pyogenic invader such as the hemolytic streptococcus or the staphylococcus If the original lesion is on the tonsil or fauces the anterior cervical nodes are more prominently involved If the posterior pharyngeal wall is primarily affected the nodes of the posterior chain are those attacked On palpation the nodes vary in size from that of a bean to a hen s egg they are often hard and tender usually with considerable perinodal involvement Unless there are secondary pyogenic invaders the nodes remain discrete and there is little tendency to suppuration When there is extreme involvement of the lymph nodes there is a veritable

General Symptoms and Signs The systemic symptoms of diphtheria vary greatly with the virulence of the infection and the site of the lesion If the local lesion is implanted on a relatively nonvascular surface as the anterior portion of the nasal septum or the larynx or trachea there is little absorption of toxin and there are few systemic symptoms If on the other hand the local lesion is implanted on a relatively more vascular site as the nasopharynx there is much greater absorption of toxin and the systemic symptoms are much more severe

The milder early systemic symptoms of diphtheria are slight fever malaise and headache As the disease becomes more severe weakness and pallor may be noted and the pulse becomes rapid usually out of proportion to the fever The temperature usually remains between 100 and 102 F by rectum but temperatures as high as 104 and 105° F may be recorded The heart usually is normal early in the disease *but it may in toxic patients develop arrythmias and other* changes manifest by electrocardiogram The clinical manifestations of heart disease early in diphtheria usually are overshadowed by the severe general toxemia that is concurrently present

Late Symptoms and Signs The late systemic manifestations of diphtheria may come on at any time during convalescence up to six or even ten weeks after the onset of the disease They are related chiefly to the nervous system and to the circulatory system The nervous system involvement is a toxic neuritis which occasionally results in generalized paralysis As there is greater concentration of toxin near the local lesion than in the systemic circulation in the acute disease and as the toxin enters the central nervous system through the myoneural junction as well as along the lymphatics the first evidence of paralysis usually is encountered in the palate and pharyngeal muscles A mild palatal paralysis without other evidences of diphtheritic neuritis is seen commonly in patients with moderately severe diphtheria who are treated on the third to the fifth day of the disease Palatal paralysis causes a change in voice with a nasal quality to phonation and regurgitation through the nose The palate may deviate to one side or hang motionless if there is complete paralysis Pharyngeal involvement produces difficulty in swallowing or complete loss of deglutition

Shortly after the onset of the palatal or pharyngeal paralysis there may be visual disturbance from involvement of the cranial nerves supplying the extra ocular muscles This results in loss of accommodation and often in diplopia Simultaneously with or shortly after the development of ocular manifestations there may be a loss of deep tendon reflexes without sensory involvement all over the body followed by weakness or paralysis of any or all striated muscles When the diaphragm and the intercostals are involved respiratory failure results Diaphragmatic paralysis can best be detected by splinting the ribs

larges by necrosis of the surrounding tissues reaching a size that varies from 2 mm to several centimeters The margin is sharply defined declivitous indurated often rolled and occasionally undermined[3] Usually there is an area of induration and discoloration of the skin about



Fig 52 Types of lesions observed in cutaneous diphtheria (Army Institute of Pathology Nos 2901 1 B and 2903 1)

the lesion The lesions almost always occur on the legs or lower portions of the body They frequently are multiple but may occur singly In some instances the diphtheria organisms may invade wounds or other abrasions of the skin All the late general manifestations of the disease may occur with cutaneous diphtheria

appear before the eighth day. In instances of early heart involvement the general toxemia usually overshadows any evidence of acute carditis. There are fever and tachycardia, but the restlessness, cyanosis and cough are more often due to the severe diphtheritic toxemia than to circulatory failure. Dehydration usually is a prominent manifestation. There is a disturbance of carbohydrate metabolism associated with the toxemia. At first this results in rapid utilization of glycogen, but later there is apparent suppression of insulin formation and an inability of the tissues to use dextrose, resulting in a low blood sugar content. The blood pressure remains normal, and the heart sounds are as a rule distinct and regular unless death is imminent.

Late circulatory failure, which usually occurs from the sixth day onward, may follow a period of apparently satisfactory convalescence. The earliest signs of involvement are given by the electrocardiogram. This will show changes in the T waves, in the conduction mechanism or in both. The abnormal T waves will be found to be either diphasic, iso-electric or inverted. The changes appear first in Lead III, later in Leads II and I. The changes in the conduction mechanism will vary in degree from slight prolongation of the PR interval to complete auriculoventricular or intraventricular block or both. As the electrocardiogram can be used only at intervals, however, it is necessary for the clinician to recognize the early clinical signs of late myocardial damage. This requires frequent auscultatory observations of the heart. At times the first sound may be split, or it may become soft and be replaced by a systolic murmur that is best heard to the left of the sternum. Any irregularity of rhythm may take place, but that most frequently encountered is a proto-diastolic gallop.

Figure 54 illustrates a case in which death occurred as a result of apparent myocardial failure.

Later during apparently good convalescence the patient may suddenly develop epigastric or precordial pain with vomiting, pallor and profuse sweating. The blood pressure may be normal or may be moderately elevated or depressed. At first there may be tachycardia, but the heart then slows and becomes irregular. If complete heart block develops, the pulse will drop to 40 or less per minute. Following heart block, death may come rapidly, or there may be a period of several days with circulatory failure. In the latter instance there will be cardiac dilatation, cyanosis, basal rales, enlargement of the liver, epigastric pain and vomiting. If there is myocardial insufficiency without block, there will be an increasing tachycardia. There may be alternate periods of bradycardia and tachycardia as heart block appears and disappears.

Associated with the late myocarditis there may be, and often is, peripheral circulatory failure. This results from a vasomotor paralysis and is brought about by involvement of the myoneural junctions or motor end plates of the parasympathetic nerves of the splanchnic

with the hand and observing the motion of the abdomen on inspiration or by placing the hands firmly below the diaphragm and palpating the movements on attempted inspiration When the diaphragm is splinted with the hands the extent of intercostal movement can best be judged through careful inspection

Figure 53 shows the course of a patient who developed complete motor paralysis seven weeks after entry into the hospital

As recovery progresses in diphtheritic neuritis there is a recession of the less severe symptoms followed gradually by improvement in

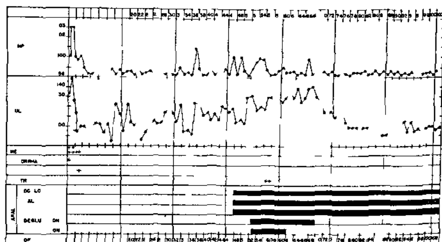


Fig 53 Temperature chart of a patient with diphtheria in whom complete motor paralysis developed

D B a Negro girl aged four was admitted on the fourth day of illness Examination *showed a membrane on both tonsils and the soft palate bloody muco-pus* coming from the nose and moderate cervical adenitis She was given antitoxin 0 000 units intramuscularly and 50 000 units intravenously and responded well although the pulse remained rapid and irregular On the sixteenth day the electrocardiogram showed slight abnormalities in the T waves and a soft systolic murmur was heard On the forty-eighth day she developed paralysis first of eyes then of palate and she also lost the deep tendon reflexes On the fifty third day she had complete respiratory paralysis and paralysis of deglutition She was treated by aspiration tube feeding and artificial respiration in a respirator She made a good recovery On discharge she had a normal electrocardiogram but palatal paralysis and absence of tendon reflexes persisted

those sites of more severe involvement Visual accommodation palatal function and the deep tendon reflexes are the last to return to normal as a rule

Cardiac manifestations in diphtheria may occur as early as the third day or after six to ten weeks have elapsed The earlier the cardiac symptoms appear the more severe they are The cardiac changes usually are the result of the action of the toxin on the myocardium and in extremely rare instances are the result of either an endocarditis or pericarditis The symptoms of early myocardial involvement usually

appear before the eighth day In instances of early heart involvement the general toxemia usually overshadows any evidence of acute carditis There are fever and tachycardia but the restlessness cyanosis and cough are more often due to the severe diphtheritic toxemia than to circulatory failure Dehydration usually is a prominent manifestation There is a disturbance of carbohydrate metabolism associated with the toxemia At first this results in rapid utilization of glycogen but later there is apparent suppression of insulin formation and an inability of the tissues to use dextrose resulting in a low blood sugar content The blood pressure remains normal and the heart sounds are as a rule distinct and regular unless death is imminent

Late circulatory failure which usually occurs from the sixth day onward may follow a period of apparently satisfactory convalescence The earliest signs of involvement are given by the electrocardiogram This will show changes in the T waves in the conduction mechanism or in both The abnormal T waves will be found to be either diphasic iso-electric or inverted The changes appear first in Lead III later in Leads II and I The changes in the conduction mechanism will vary in degree from slight prolongation of the PR interval to complete auriculoventricular or intraventricular block or both As the electrocardiogram can be used only at intervals however it is necessary for the clinician to recognize the early clinical signs of late myocardial damage This requires frequent auscultatory observations of the heart At times the first sound may be split or it may become soft and be replaced by a systolic murmur that is best heard to the left of the sternum Any irregularity of rhythm may take place but that most frequently encountered is a proto-diastolic gallop

Figure 51 illustrates a case in which death occurred as a result of apparent myocardial failure

Later during apparently good convalescence the patient may suddenly develop epigastric or precordial pain with vomiting pallor and profuse sweating The blood pressure may be normal or may be moderately elevated or depressed At first there may be tachycardia but the heart then slows and becomes irregular If complete heart block develops the pulse will drop to 40 or less per minute Following heart block death may come rapidly or there may be a period of several days with circulatory failure In the latter instance there will be cardiac dilatation cyanosis basal rales enlargement of the liver epigastric pain and vomiting If there is myocardial insufficiency without block there will be an increasing tachycardia There may be alternate periods of bradycardia and tachycardia as heart block appears and disappears

Associated with the late myocarditis there may be and often is peripheral circulatory failure This results from a vasomotor paralysis and is brought about by involvement of the myoneural junctions or motor end plates of the parasympathetic nerves of the splanchnic

vessels It is a part of the polyneuritis and usually comes on simultaneously with the other evidences of polyneuritis and paralysis According to Wesselhoeft[26] this is the commonest vascular syndrome occurring in diphtheria and even in the presence of advanced myocardial damage tends to overshadow disorders arising within the heart The clinical manifestations are marked pallor producing an ashen gray or alabaster like color The patient especially if he is a child develops a peculiar and characteristic frightened look The skin be

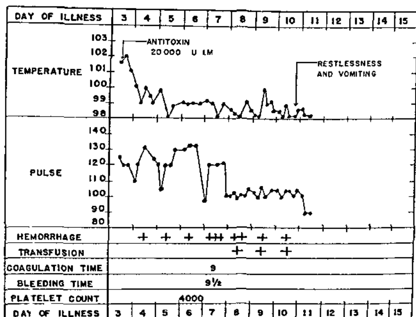


Fig 54 Temperature chart of a patient with diphtheria who died as a result of myocardial failure

C W a white girl aged three was admitted on the third day of illness There was a membrane over both tonsils the uvula and part of the soft palate moderate cervical adenitis and moderate bleeding from slight trauma during the examination Antitoxin was given in a do e of 20 000 units intramuscularly Nasal hemorrhages occurred on the fourth day and purpura of the skin on the sixth day The blood showed prolonged bleeding and clotting times no clot retraction and a reduction in the platelet count The patient was treated with small repeated tran fusions The pulse slowed and the patient died suddenly apparently of myocardial failure Necropsy was not obtained

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Irritability of the pace maker which causes evening tachycardia

persistent relative tachycardia bradycardia or effort syndrome is a mild but annoying cardiovascular disorder occasionally encountered in the late convalescent stage of diphtheria[14] It may persist for one to two months It may have its origin in the sinus node or in parasympathetic vagus nerves

Complications

These usually are limited to the respiratory tract *Bronchopneumonia is by far the most serious* This usually is a mixed type of infection from secondary invaders more commonly the beta hemolytic streptococcus or the pneumococcus Occasionally particularly when there is extensive tracheobronchial diphtheria the pneumonia may be due *only to the diphtheria bacillus Pneumonia more frequently follows* laryngeal diphtheria especially in patients who have required tracheotomy

The symptoms are continued elevation of temperature and pulse with rapid respirations a reversal of the normal respiratory rhythm producing a pause after inspiration followed by an expiratory grunt The physical findings are those of a diffuse bronchopneumonia Often the most reliable diagnostic sign is the rapid grunting respiration commonly with cyanosis There may be areas of dullness to percussion and medium and fine crepitant rales on auscultation Breath sounds show little variation from the normal except in patients with confluent involvement when they become bronchial in character There is usually a polymorphonuclear leukocytosis with a shift to the left The roentgenogram may show scattered areas of infiltration but even in well marked cases it may appear entirely normal

Otitis media is seen frequently in diphtheria It may occur at any time even well into convalescence though it usually is present in a catarrhal form from the beginning It probably results from secondary invading pyogenic organisms being caught in the occluded eustachian tube with peripheral propagation Occasionally the diphtheria bacillus is the only infecting organism The symptoms of otitis media are those of fever and restlessness and in older children otitic pain The diagnosis must be made by inspection of the tympanic membrane

Laboratory Examinations

If diphtheria is suspected in a patient the organisms may be identified almost immediately by examining a film from the lesion stained by Ponder s or any other differential stain However much more certain diagnoses can be established by making proper cultures These are obtained by the use of cotton tipped applicators applied under the margins and over the surface of the false membrane The applicator is then passed lightly over the surface of Loeffler s serum slants or preferably over tellurite agar since the colonies growing on the

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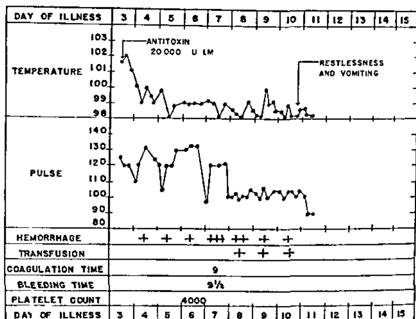


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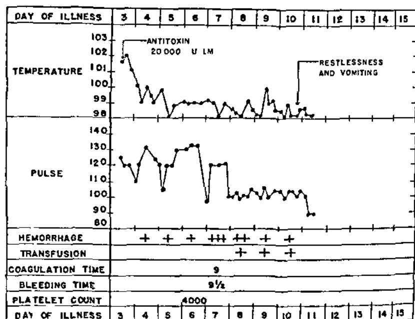


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spection with *full depression of the tongue* The diphtheritic membrane if early may be in multiple foci resembling a follicular tonsillitis and it may be thin and transparent In this stage there will be considerable injection of the pharynx Thereafter the lesions coalesce more or less rapidly and the false membrane may become thicker The characteristic color of the false membrane will be a grayish white but little stress can be laid on the color per se as virulent diphtheria bacilli may be cultivated from lesions that vary from dead white to cream greenish gray dark brown green or black *The darker colors usually depend upon hemorrhage into the lesion or upon the presence of* secondary invading organisms

The location of the lesion is of considerable importance While diphtheria may often be bilateral it is not uncommon to have a unilateral lesion This is extremely suggestive since most of the simulating *diseases produce bilateral lesions* Again diphtheria may be and often is confined to the area of the tonsils As a rule however as the lesion spreads it transgresses the borders of the lymphoid tissue and appears on the pillars the lateral or *posterior* pharyngeal wall or on the palate and uvula The diffuse spread is not found characteristically in other conditions There usually is no ulceration of the throat in diphtheria as may be found in Vincent s infection There is a rather characteristic fetid odor in patients with diphtheria that may be an aid to diagnosis

The general symptoms of diphtheria are fairly characteristic The fever while it may be high from the effect of secondarily invading organisms *is usually slight or moderate The pulse however is* unduly rapid and in many instances shallow There often is considerable pallor of the skin and mucous membranes

Differential Diagnosis of Pharyngeal Diphtheria The greatest difficulty in the differential diagnosis of pharyngeal diphtheria is in relation to follicular tonsillitis peritonsillar abscess scarlet fever Vincent s angina syphilis infectious mononucleosis and rarely in the bullous type of erythema multiforme

Follicular tonsillitis often causes confusion in the diagnosis of diphtheria In both diseases the tonsils are intensely injected and may be covered with minute areas of exudate or with a membrane In the stage of diphtheria in which this confusion is more likely to exist the membrane more often will be of a pearly gray character rather than the yellowish pus of follicular tonsillitis and the diphtheritic membrane will be less easily dislodged than will the exudate of tonsillitis In tonsillitis the fever is high while in diphtheria it is slight or moderate *Albuminuria is frequently present in diphtheria with moderate fever* but occurs early in follicular tonsillitis only when there is a high fever However in many instances a clinical diagnosis cannot be made If there is a history of contact or if the lesion is present in a young non

latter suggest the type of diphtheria bacillus (whether *gravis inter medius* or *mitis*) and this information may be useful in clinical inter pretation After twelve to twenty four hours incubation the cultures are identified by microscopic examination and also by colony form on the more sensitive and specific tellurite plates [9]

A more rapid culture diagnosis may be made[2] by taking the culture on a sterile cotton swab impregnated with sterile undiluted and un heated horse serum to which no preservative has been added and which has been flamed lightly to obtain a surface coagulum Cultures are obtained in the usual manner the swabs are incubated for from two to four hours either in an incubator or in a vest pocket and smears are made directly from the swabs Accurate results are obtained quickly

In laryngeal diphtheria without pharyngeal involvement cultures taken from the nasal passages and pharynx are unreliable and frequently give false negative results In this situation as in all others cultures should be taken directly from the area involved It is also important to remember that a negative culture does not exclude diphtheria nor does a positive culture establish the diagnosis in all cases About one fifth of the initial cultures taken from patients with clinical diphtheria are negative Healthy carriers of virulent diphtheria bacilli are common However in the presence of an acute inflammatory process and a culture positive for *C diphtheriae* the patient must be treated as if he had diphtheria until there is definite proof to the contrary

The tellurite reaction by which a cotton tipped applicator dipped in a 2 per cent potassium tellurite solution in 40 per cent glycerine gives a dark color to the membrane when touched onto the false membrane without touching the tongue was first introduced by Man zullo [13] More recent investigations[12] cast serious doubt on the relia bility of this reaction since false negative reactions were obtained in 16 per cent of 100 consecutive cases studied Several investigators also report a high percentage of false positive reactions

There is no typical hemogram in diphtheria the leukocytic response varying with the severity of the disease Diphtheria does not alter the skin reaction to the tuberculin test

Diagnosis

The diagnosis of diphtheria depends primarily upon an accurate history and a complete physical examination Since the throat symp toms may be slight it is most important that a careful inspection of the throat be made an integral part of every examination As most young children object rather violently to having their tongue depressed deeply it is preferable to complete the rest of the examination before inspecting the throat This should be done gently at first often with out the use of a tongue blade until all information to be so gained can be achieved This must be followed by a complete but brief in

when there is a high fever while it is a frequent early manifestation of diphtheria As in acute follicular tonsillitis the diagnosis frequently can be made only by bacterial culture In this situation if the disease has been present for over forty-eight hours the patient should be treated for diphtheria without awaiting a conclusive diagnosis

Vincent's angina frequently simulates diphtheria There often is a greenish gray pseudomembrane that closely resembles the local lesion of diphtheria This usually is confined to the surface of the tonsil however or at most to the lower edge of the palate and the uvula There is frequently an ulceration so that the surface of the pseudomembrane is below the surface of the true mucous membrane If the membrane is scraped off it is removed with great difficulty and the site usually bleeds freely As a rule there are associated ulcers on the gums or the buccal mucosa Scrapings from these lesions when stained for ten or fifteen minutes with 1 per cent methylene blue show the typical fusiform bacilli and spirillae Furthermore there is more fever than is usual in diphtheria the pulse is less rapid and albuminuria rarely is present

Syphilis can also produce lesions closely resembling those of diphtheria In syphilis the lesions usually are multiple and ulcerative and in the majority of patients they will be associated with a secondary syphilitic rash The temperature and pulse as a rule will be normal The diagnosis can be proved conclusively by dark field examination

Infectious mononucleosis is more commonly confused with diphtheria than is generally recognized The disease frequently starts with a severe angina often with a patchy exudate on the tonsils or on the lymphoid tissue of the pharynx General lymphadenopathy usually is present If the oral lesions persist after adequate serum therapy for diphtheria and particularly if cultures are found to be negative for diphtheria careful hematologic and heterophil antibody studies should be made to exclude infectious mononucleosis

The bullous type of *erythema multiforme* is a rather rare disease although many such patients are reported from isolation hospitals where they have been sent because of suspected diphtheria There are extensive oral lesions as almost the whole buccal mucosa is necrotic with a gelatinous appearance The appearance suggests that the buccal mucosa the tongue and the pharynx have been bathed in a strong solution of lye The diagnosis is confirmed by the finding of the bullous lesions on the body and by the distinctly different oral pathology

Differential Diagnosis of Laryngeal Diphtheria The most serious condition that must be differentiated from laryngeal diphtheria is acute laryngotracheitis or tracheobronchitis Like diphtheria this is an affliction of young children The temperature is higher as a rule and there is a greater leukocytosis There is the same aphonia however and in severe instances the same evidence of respiratory obstruction

immunized child it usually is safer and more conservative to give antitoxin immediately while in other patients it usually is safe to await the results of culture If this latter course is elected the throat should be inspected again within six to twelve hours to observe the progression of the lesion If the follicles are becoming coalescent treatment for diphtheria should be instituted immediately

Peritonsillar abscess usually causes little doubt as to diagnosis The patient has great difficulty opening his mouth and there is marked *unilateral* swelling of the pharynx We have seen diphtheria combined with peritonsillar abscess however and if there is a membrane that will not remove easily with a swab cultures should be made and the *patient should be given the benefit of serum therapy* The operative scar after incision of the peritonsillar abscess often resembles diphtheria as does the operative site after tonsillectomy In these conditions however the membrane does not progress beyond the border of the wound and a short period of observation will clarify the diagnosis

Scarlet fever may present serious difficulties in the diagnosis of diphtheria In this disease there often is an apparent membrane on the medial surface of the tonsils that closely resembles that of diphtheria In such patients there usually are a high fever a well defined scarlatiniform rash and characteristic oral findings The latter include a strawberry tongue enantham on the palate and accentuated perifaucial injection and are quite characteristic of scarlet fever

However while there may be no difficulty in diagnosing scarlet fever the two diseases may be present concurrently and the problem of eliminating the possibility of diphtheria is extremely acute In such a situation if there is a faucial membrane that does not wipe off easily or that extends beyond the tonsillar margins the patient should be treated as having concurrent diphtheria and scarlet fever In those patients with scarlet fever in whom there is lesser toxemia or in whom the typical scarlatiniform rash is not present the tongue will show desquamation around the edges after the second or third day and complete desquamation with the typical raspberry appearance with *enlarged papillae after the fourth or fifth day Earlier in the course* there usually is a punctate enanthem on the soft palate and the fauces are finely injected with a marked perifaucial accentuation of the redness Furthermore the exudate on the tonsils in scarlet fever usually is soft and wipes off with ease In diphtheria on the other hand there is less redness of the fauces and pharynx especially a short distance beyond the membrane there is an absence of the punctate mottling of the soft palate and the tongue while often coated fails to show the enlarged papillae The presence or absence of cervical adenitis is of little significance as it may be present in both diseases Albuminuria may occur in *both* diseases but it occurs early in scarlet fever only

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The differentiation usually can be made only by direct laryngoscopic examination in which the examiner will see an acutely injected larynx instead of the diphtheritic membrane often with tenacious mucopurulent exudate from the trachea Cultures from the larynx should be taken immediately and inoculated on both a Loeffler s slant and on tellurite agar and blood agar plates If there is any doubt as to the etiologic diagnosis or if facilities for laryngoscopic examination are lacking diphtheria antiserum should be given immediately

Spasmodic croup often causes concern in the diagnosis of laryngeal diphtheria The condition comes on at night however suddenly in an otherwise well child—a train of symptoms rarely seen in diphtheria If there is a history of previous attacks between which the child has been apparently well it usually is safe to rely on palliative measures until the results of culture can be obtained

Simple laryngitis such as that seen in common respiratory infections or antedating measles or pertussis often suggests diphtheria There usually will be rhinorrhea however and in measles Koplik spots and lacrimation will be present Congenital laryngeal stridor is found only in very young infants and will date from birth The infant will be in normal health except for the laryngeal crow Acute laryngospasm is a part of and will be associated with other evidences of tetany These are carpopedal spasm a positive Chvostek sign and rachitic beading of the ribs Retropharyngeal abscess should be recognized by careful physical examination This must include digital palpation of the posterior pharynx Also if flexion of the neck produces respiratory obstruction a retropharyngeal abscess is strongly indicated Edema of the glottis can also be recognized by careful physical examination including direct visualization of the larynx A foreign body should be suspected if there is a sudden onset of dyspnea If the foreign body is radiopaque it may be recognized by x ray examination In doubtful cases laryngoscopy or bronchoscopy must be performed

Prognosis

At the present time the prognosis of diphtheria varies inversely with the duration of the disease before treatment and the age of the patient It is altered remarkably by the extent and location of the lesion and by the type of infecting organism Fortunately infection with the *gravis* type of *C diphtheriae* is rare in the United States a fact that contributes materially to the better prognosis here

In the preantitoxin days according to Ker[10] the fatality rate from diphtheria varied from 20 to 10 per cent with 20 to 25 per cent being expected in good hospitals Recently Togasaki[24] has reported only 4 8 per cent deaths among 753 patients The fatality rate varied from 41 6 per cent for infants under one year to 2 5 per cent for patients aged ten to fifteen years (Table 47)

The duration of illness before treatment is of extreme importance in formulating the prognosis in any given patient. For those individuals who receive adequate therapy within the first three days of the disease

TABLE 47

CASE FATALITY AMONG 3 PATIENTS WITH DIPHTHERIA

Age (years)	*Number of Patients*	*Number Died*	*Case Fatality (per cent)*
Less than 1	1	5	41
1-4	2 9	18	8
5-9	218	9	4 1
10-14	80	[illegible]	3
15 and over	214	2	0 9
Total	3	36	4 8

Among 54 patients with bull neck there were 1 deaths. Among 54 patients with respiratory obstruction 48 had tracheotomy. Among these 48 there were deaths.

the mortality is remarkably low while the greater the duration over three days the more serious the outlook (Table 48). Patients who have been ill for one week or more without antitoxin survive only if

TABLE 48

FATALITY RATES FROM DIPHTHERIA ACCORDING TO THE DAY ON WHICH SERUM WAS FIRST INJECTED IN 8 91 CONSECUTIVE CASES

Day of Illness	*Patients*	*Deaths*	*Percentage of Mortality*
First	3 9	5	1
Second	69		3 39
Third	2407	16	6 8
Fourth	161	1	10 91
Fifth	911	136	14 92
Sixth	416	54	12 98
Seventh	3 0	53	16 56
Later	3 7	50	1 9
Total	8 91	16	8 33

their infection is in a relatively nonvascular situation or if the infecting organism is feeble. The reason for this is that once toxin has been fixed in the tissues it is beyond the reach of antitoxin. If there

has been extensive absorption of toxin the outlook for the patient is much worse

The location and character of the lesion are also of great significance in prognosis In the cases reported by Togasaki[24] there were fifty four with respiratory obstruction Among these tracheotomy was done on forty eight of whom twenty two died The larynx is relatively nonvascular however with little absorption of toxin Therefore the incidence of heart failure and paralysis is rare in these patients and if they survive tracheotomy their prognosis is good

The nasopharynx on the other hand is quite vascular allowing free absorption of toxin The incidence of myocarditis and paralysis is much greater especially if treatment is delayed and the mortality is much greater (Table 49)

TABLE 49

INCIDENCE OF PARALYSIS ACCORDING TO THE DAY OF FIRST INJECTION OF ANTITOXIN [10]

Day of Illness	*Patients*	*Cases of Paralysis*	*Percentage*
First	142	3	2 1
Second	1026	53	5 1
Third	1015	98	9 6
Fourth	651	93	14 2
Fifth	356	36	10 1
Sixth	134	19	14 1
Seventh	119	13	10 9
Later	115	5	4 3
Total	3558	320	8 9

Cardiac cases with no other form of paralysis are excluded

Physical findings that indicate a severe infection are hemorrhages bull neck and shock Hemorrhages in diphtheria are of two types true purpura with massive subcutaneous hemorrhage and hemorrhage from the mucous membranes only The former indicates an almost invariably fatal process the latter a very severe disease though with some chance of recovery Bull neck may be due to either the diphtheria toxin or to secondary invaders It is of grave prognostic import Among fifty four such patients in one series[4] there were twenty-one deaths The prompt use of chemotherapy in combination with antitoxin however may brighten the outlook for these patients

Many patients who do not receive treatment for diphtheria until late in the acute phase of the disease present a picture of shock when

they are seen They are pale and waxy with a rapid feeble pulse and a low blood pressure This usually is evidence of either severe toxemia or myocardial failure and is an extraordinarily bad prognostic omen The occurrence of heart failure later in diphtheria is also of grave importance though if it is detected early by electrocardiogram and is treated appropriately the outcome is much more favorable than if it is allowed to develop until it can be recognized clinically Paralysis is an extremely annoying complication but rarely threatens life if there are facilities for the treatment of paralysis of respiration and deglutition

There is one final factor of the utmost importance in the prognosis of diphtheria Treatment must be early for maximum effect and yet treatment must follow diagnosis There is at present a most regrettable tendency on the part of many practitioners to administer sulfonamides or penicillin to all patients with sore throats often without careful examination This results in delayed diagnosis and an increased mortality that would be preventable if due care were exercised

Prevention

This may be secured by either active or passive immunization Active immunity is induced by the administration of toxin antitoxin mixtures or of toxoid The toxoid may be given in the fluid form or after alum precipitation Toxin antitoxin has been replaced to a large extent by toxoid The chief disadvantages of toxin antitoxin were the slow and somewhat uncertain development of immunity and the danger of sensitization to serum from the antitoxin used Both these disadvantages are overcome by toxoid although reactions are more frequent especially in adults and in children over seven or eight years of age Systemic reactions to toxoid are extremely rare in infants and young children though there may be local redness and induration and slight fever for one day When alum precipitated toxoid is used a local subcutaneous lump may persist for several weeks Occasionally such local lesions suppurate and cause sterile abscess

The current practice of the writer is to give an active immunity to all infants in the second half year of life preferably beginning at the seventh month by injecting three doses of alum precipitated toxoid at monthly intervals (For convenience a combination of diphtheria and tetanus toxoids and pertussis vaccine is used since an immunity to all these diseases should be induced and since immunity to multiple antigens is induced as well or better when they are given in combination as when they are given separately [11] [17] Reactions to the combination seem to be no greater than to the individual antigen)[2*] The dosage is adjusted to contain one immunizing dose as standardized by the National Institute of Health and varies from 0 5 cc to 1 0 cc depending on the potency of the particular product used Booster doses

has been extensive absorption of toxin the outlook for the patient is much worse

The location and character of the lesion are also of great significance in prognosis In the cases reported by Togasaki[4] there were fifty four with respiratory obstruction Among these tracheotomy was done on forty eight of whom twenty two died The larynx is relatively nonvascular however with little absorption of toxin Therefore the incidence of heart failure and paralysis is rare in these patients and if they survive tracheotomy their prognosis is good

The nasopharynx on the other hand is quite vascular allowing free absorption of toxin The incidence of myocarditis and paralysis is much greater especially if treatment is delayed and the mortality is much greater (Table 49)

TABLE 49

INCIDENCE OF PARALYSIS ACCORDING TO THE DAY OF FIRST INJECTION OF ANTITOXIN[10]

Day of Illness	*Patients*	*Cases of Paralysis*	*Percentage*
First	142	3	2 1
Second	1026	53	5 1
Third	1015	98	9 6
Fourth	651	93	14 2
Fifth	356	36	10 1
Sixth	134	19	14 1
Seventh	119	13	10 9
Later	115	5	4 3
Total	3558	320	8 9

Cardiac cases with no other form of paralysis are excluded

Physical findings that indicate a severe infection are hemorrhages bull neck and shock Hemorrhages in diphtheria are of two types true purpura with massive subcutaneous hemorrhage and hemorrhage from the mucous membranes only The former indicates an almost invariably fatal process the latter a very severe disease though with some chance of recovery Bull neck may be due to either the diphtheria *toxin or* to secondary invaders It is of grave prognostic import Among fifty four such patients in one series[24] there were twenty-one deaths The prompt use of chemotherapy in combination with antitoxin however may brighten the outlook for these patients

Many patients who do not receive treatment for diphtheria until late in the acute phase of the disease present a picture of shock when

they are seen. They are pale and waxy, with a rapid, feeble pulse and a low blood pressure. This usually is evidence of either severe toxemia or myocardial failure and is an extraordinarily bad prognostic omen. The occurrence of heart failure later in diphtheria is also of grave importance though if it is detected early by electrocardiogram and is treated appropriately the outcome is much more favorable than if it is allowed to develop until it can be recognized clinically. Paralysis is an extremely annoying complication but rarely threatens life if there are facilities for the treatment of paralysis of respiration and deglutition.

There is one final factor of the utmost importance in the prognosis of diphtheria. Treatment must be early for maximum effect, and yet treatment must follow diagnosis. There is at present a most regrettable tendency on the part of many practitioners to administer sulfonamides or penicillin to all patients with sore throats, often without careful examination. This results in delayed diagnosis and an increased mortality that would be preventable if due care were exercised.

PREVENTION

This may be secured by either active or passive immunization. Active immunity is induced by the administration of toxin antitoxin mixtures or of toxoid. The toxoid may be given in the fluid form or after alum precipitation. Toxin antitoxin has been replaced to a large extent by toxoid. The chief disadvantages of toxin antitoxin were the slow and somewhat uncertain development of immunity and the danger of sensitization to serum from the antitoxin used. Both these disadvantages are overcome by toxoid, although reactions are more frequent, especially in adults and in children over seven or eight years of age. Systemic reactions to toxoid are extremely rare in infants and young children, though there may be local redness and induration and slight fever for one day. When alum precipitated toxoid is used, a local subcutaneous lump may persist for several weeks. Occasionally such local lesions suppurate and cause sterile abscess.

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are given at two years and when the child enters school These are necessary because the immunity originally developed is not permanent but subsides gradually over a few years time Immunity is stimulated rapidly by such repeated injections

If immunization is needed by patients of eight years or over, alum precipitated toxoid is abandoned in favor of fluid toxoid A preliminary test of sensitivity of the patient to toxoid is made by injecting 0 1 cc of toxoid diluted 1 20 in saline solution intradermally [15] If there is a local area of redness of 1 cm diameter or more within three days after the injection the patient is sensitive to the toxoid In such a situation the patient may be immunized by graduated doses of toxoid beginning with 0 1 cc subcutaneously Injections should be made at intervals of five to ten days and should be increased gradually to 0 2 cc 0 3 cc 0 5 cc and so on depending upon the amount of reaction until the complete immunizing dose is given If there is no reaction to the intracutaneous test within three days the injections may be given in full amounts usually three injections of 1 0 cc each at fourteen to thirty day intervals If there is a severe reaction to the skin test and to the first subcutaneous dose of 0 1 cc it is well to test for sensitivity to a toxin antitoxin mixture or to abandon the projected active immunization entirely

After the completion of a course of active immunization the state of immunity in the patient should be determined by a Schick test [20] This is done by injecting intradermally 0 1 cc of isotonic salt solution containing 1/50 minimum lethal dose of diphtheria antitoxin This is best done with a tuberculin syringe through a 27 gauge needle The test should be read in five to seven days or if a control test of heat inactivated toxin is used after forty eight hours A positive test is indicated by an area of induration and discoloration of 1 0 cm or more at the site of the injection Staining at the site of a positive Schick test may persist for weeks but eventually disappears A positive test indicates that the patient is susceptible to diphtheria A negative Schick test as demonstrated by Pham [19] means that the patient either has circulating antibody in the blood adequate in amount to neutralize the toxin or has the ability to produce such antibody rapidly and thus indicates an immunity to diphtheria

Passive immunity to diphtheria may be induced by injecting antitoxin in doses of 1000 to 2500 units subcutaneously or intramuscularly This gives a temporary immunity that lasts for two or three weeks in most patients though diphtheria has occurred as early as the seventh day after such a dose This procedure is used principally to protect contacts of diphtheria patients in communities where adequate facilities for immediate cultural studies are not available

The present concept of the management of contacts with patients suffering from diphtheria is as follows a Schick test should be done

immediately on all patients. At the same time nose and throat cultures should be made as outlined on page 391 (laboratory diagnosis). Repeat nose and throat cultures should be made on all contacts at intervals of twenty four to forty-eight hours until at least three negative cultures have been reported *after the last contact* with a case or carrier. If positive cultures are obtained on Schick positive individuals, antitoxin in therapeutic doses should be administered immediately (at least 10,000 units intramuscularly). If positive cultures are obtained on Schick negative individuals they should be isolated as carriers until their carrier state has been eliminated.

TREATMENT

The major objectives in the treatment of diphtheria and the agents to attain them are as follows

Objective	*Agent*
Neutralization of toxin	Antitoxin
Control of secondary infection	Penicillin and/or Sulfonamides
Decrease of systemic effect of toxin	Dextrose intravenously
	Absolute rest
Rest	Mild sedatives
	Quiet
Maintenance of a clean airway	Aspiration
	Intubation
	Tracheotomy

As has been emphasized and re-emphasized, the successful application of these therapeutic techniques requires early diagnosis. This in turn requires a complete history and physical examination at the earliest possible moment. In practically all patients treatment should be based on clinical appraisal alone. While bacteriological culture is extremely important for confirmation of diagnosis, in only rare instances is it safe to delay specific treatment until the bacteriological diagnosis has been made.

Antitoxin. The only specific treatment for diphtheria is the antitoxin. This is the only agent that will neutralize the toxin of diphtheria and its use early in the disease is imperative. The dosage employed varies with the duration of the disease, the site and extent of the lesion and the general condition of the patient. The rule of thumb schedule now employed at the Gallinger Municipal Hospital is outlined in Table 50. These dosages are considerably higher than those recommended by the older writers[4, 10] but there is no known harm from even more massive doses of antitoxin. Since the virulence of the organism is never known when the antitoxin is being given, it is thought best to give adequate amounts to neutralize the maximal quantities of circulating antitoxin. The full dose should be given initially. A repeat dose is rarely used.

There are several factors of importance to be remembered in ad

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in these situations they should be given in the same dosage as that in which they are employed in similar conditions in patients not suffering from diphtheria

Penicillin *C diphtheriae* is slightly sensitive to the action of penicillin[8] Penicillin does not neutralize the diphtheria toxin however and it cannot be relied on as the treatment of choice We have seen several patients who were given penicillin before the diagnosis of diphtheria was made In no instance among those seen did the drug appreciably alter the course of the disease This experience has been shared by others[-5] Penicillin in doses of 20 000 to 30 000 units every three hours however will eliminate or greatly reduce the bacterial complications of diphtheria but it will not affect the late manifestations of the disease that are due to the action of diphtheria toxin[7]

The experience in treating the diphtheria carrier state with penicillin has been variable Karelitz[7] gave doses of 20 000 units of penicillin every two to three hours to eighty patients with diphtheria The drug was continued until three successive negative cultures were obtained and was resumed immediately if positive cultures were obtained within five days after the drug was stopped By this method 92 5 per cent of eighty patients carrying the diphtheria bacillus during convalescence had permanently negative cultures within ten days after the onset of treatment This was in contrast to 7 8 per cent negative cultures within the same time among forty two control cases and 35 per cent of 457 patients treated without penicillin by other observers Hodes[25] on the other hand found that penicillin made little if any difference in the treatment of approximately 200 patients with diphtheria

Intravenous Dextrose Solution One of the most important adjuncts to serum therapy is intravenously administered dextrose solution This is used in an attempt to mitigate the effects of the toxin on the more vital structures of the body The use of dextrose stems from the work of Schwentker[21] As outlined above in diphtheria there is a general toxemia with not only neuritis and myocarditis but also toxic nephritis hepatitis and involvement of all other tissues of the body There is a disturbance of carbohydrate metabolism including glycogen storage so that there is at first a severe hypoglycemia and later a hyperglycemia This leads to secondary interference with the nutrition of the more vital organs as the heart and the central nervous system The use of a high protein high carbohydrate diet and of intravenous dextrose solution helps overcome the disturbed carbohydrate balance and promotes better metabolism generally (The use of plasma or amino acid solutions to aid in this process has not been tried) Intravenous dextrose solution is used therefore in all patients with extensive nasopharyngeal diphtheria in those with extensive cervical adenitis hemorrhage or severe albuminuria and in those patients who are treated after the third day of illness In ulin to cover the dextro e

ministering diphtheria antitoxin The antitoxin is contained in horse serum and while the newer methods of preparation have greatly lessened the dangers of serum reaction they have not eliminated these dangers To further minimize the hazards of the administration of this foreign protein the patient must *always* be tested for possible serum sensitivity before antitoxin is given This procedure is given on page 33

The choice of the route of administration of serum merits comment The usual procedure in mild or early cases of diphtheria is by intramuscular injection It should be remembered however that the antitoxin is absorbed slowly when it is given by this route and that the maximum blood concentration is attained only after ten to twenty four hours Therefore the local lesion of diphtheria may enlarge during this time and when seen the following day the membrane may be more extensive than when the treatment was given For this reason if there is danger to the patient from a slight spread of the membrane or from the continued circulation of free toxin at least half of the serum must

TABLE 50

Recommended Schedule of Antitoxin Dosage

Site of Lesion	*Dosage in Units (times 1000)*	*Route of Administration*
Nose	5–10	Intramuscular
Tonsils	10–20	Intramuscular
Tonsils and pharynx (early)	30–60	Intramuscular and intravenous
Larynx	30–40	Intramuscular and intravenous
Larynx and pharynx	50 100	Intramuscular and intravenous
Bull neck or with hemorrhage	80–150	Intramuscular and intravenous
Late (after 3 days)	80–200	Intramuscular and intravenous

be given by intravenous injection The intravenous route is used in laryngeal diphtheria in extensive nasopharyngeal involvement when there is extensive cervical adenitis when hemorrhage is present and in all patients treated after the third day of illness In our opinion even when all tests for serum sensitivity are negative it is preferable to give the serum diluted with at least twice its volume of isotonic salt solution or with 10 per cent solution of dextrose Some authorities advise against the use of dextrose to dilute serum because a fine precipitate may form that will either block the needle or cause a reaction in the patient We have not encountered these difficulties and since the majority of our patients who require intravenous serum also require dextrose have used this diluent frequently

Sulfonamides These drugs have no influence on the diphtheria bacillus and must not be relied upon for the treatment of diphtheria [23] They are of value in treating secondary bacterial invasion or the bacterial complications such as pneumonia or otitis media When used

is made at least once a week with electrocardiographic tracings and a complete neurological appraisal If by these standards the patient is found to be free from all cardiac and nervous manifestations at the end of six weeks it usually will be safe to allow him to have moderate graduated activity even though such manifestations may appear several weeks later In that instance they will be less severe and can be recognized and treated before serious consequences develop

Treatment of Laryngeal Diphtheria All patients with laryngeal diphtheria as well as those with respiratory obstruction in whom diphtheria cannot be ruled out should have the same treatment as that outlined above The exceptions to this policy are those dependent upon the fact that there is less toxic absorption from the larynx than from the pharynx Intravenous dextrose solution and the most rigid rest usually are not required in a patient with the local lesion confined to the larynx Because of the dangers of suffocation from a slightly expanding lesion however all patients with laryngeal involvement should be given at least half their antitoxin by the intravenous route

The need to avoid sedation in patients with laryngeal diphtheria merits special comment In these patients respiratory obstruction with consequent respiratory failure from exhaustion is an ever present possibility and menace If sedatives are used in such patients the evidences of exhaustion often are masked as are many of the evidences of obstruction It behooves the careful physician therefore to soothe the child by other means and to avoid all sedation with the greatest care Opiates are absolutely banned and even the mildest of sedatives are to be used only under the most pressing circumstances

The ideal treatment of respiratory obstruction from laryngeal diphtheria in a large well equipped hospital has been outlined by Neffson [19] This includes frequent gentle aspiration of the larynx through direct laryngoscopy whenever evidences of obstruction to respiration or of exhaustion become evident Suction should be used whenever loose membrane mucopurulent exudate or other removable material is causing the obstruction Intubation by direct visualization should be used when the obstruction is caused by subglottic edema Tracheotomy is used when the intubation tube is repeatedly blocked or coughed up or when the tube cannot be removed within three weeks time The *successful application of this treatment requires a skilled laryngoscopist* to be *immediately* available at all times Since many hospitals treat too few patients with this disorder to warrant the maintenance of a trained laryngoscopist on immediate call at all times the procedures that may be used in them are somewhat different

All patients with laryngeal involvement are placed in a steam tent and given moderate doses of expectorant drugs If there is any doubt as to the diagnosis laryngoscopic examination is done After sensitivity tests they are given antitoxin 20 000 to 40 000 units with half the

one unit for each one or two grams of dextrose is advocated by some physicians but is of questionable value We do not use it

The dextrose solution may be given in concentrations ranging from 10 per cent to 50 per cent but as these patients usually require considerable amounts of fluid to prevent or correct dehydration the lesser concentration is more frequently employed Our practice is to give young children injections up to 10 cc per pound of body weight (20 cc per kg) twice a day until the evidences of toxemia begin to lessen considerably then once a day for several more days This treatment is rarely employed for more than a week or ten days The maximum amount of solution given at one time to a child of five or six is 250 to 300 cc Enough isotonic salt solution is given along with the dextrose to supply the major electrolyte needs This is 1 gm a day for a child of one year and 2 gm for a child of five

Rest All patients with diphtheria should have complete bed rest This is essential to reduce the metabolism of the patient and thereby to minimize the effect of the toxin on the critical tissues If the patient is restless or in pain mild sedatives may be used to promote rest These include bromides chloral hydrate paraldehyde or some of the more rapidly acting barbiturates They should be used with caution however and never in the presence of respiratory obstruction (see the following section) The more potent drugs especially morphine should be avoided assiduously as they may cause too marked depression of the patient

In patients with severely toxic diphtheria the rest should be complete with the recumbent position being maintained This also should include careful nursing of the patient with no voluntary motions allowed him The patient should be attended hand and foot He should be fed bathed and treated with the utmost caution This extreme solicitude must be maintained for two or three weeks when myocarditis may be sudden in onset and lethal in effect During this time electrocardiographic tracings should be made frequently at least once a week If the tracings are normal after two or three weeks the rigid precautions may be relaxed slightly but bed rest must continue to be enforced

The length of the patient s rest period depends upon the duration and severity of symptoms at the time of admission In our opinion two weeks is a minimal period of rest for any patient with clinical evidences of faucial diphtheria In mild uncomplicated cases of tonsillar nasal or laryngeal diphtheria also this period is adequate In those patients who have more severe nasopharyngeal involvement however especially if there is marked cervical lymphadenopathy a hemorrhagic tendency or evidences of shock at the time treatment is given the period of rest must be prolonged up to eight or ten weeks or more Since the more prolonged periods of rest are required by the late manifestations of diphtheria careful re-evaluation of all such toxic patients

through the day and remove the tube at night The following day if the patient still is unable to swallow the tube is re-inserted through the other nostril This interrupted use of the stomach tube is resorted to to prevent erosion and ulceration of the mucous membrane by the tube

If there is paralysis of the muscles of respiration the patient should be placed in a mechanical respirator and treated exactly as if he had poliomyelitis involving these same muscles Figure 53 shows a patient successfully treated in this way These patients and those with lesser degrees of paralysis should have bed rest until their paralysis disappears and there is a return to normal of all tendon reflexes

The myocarditis of diphtheria can be treated best by the prophylactic intravenous administration of dextrose solutions in the toxic stages of the disease to minimize the effect of the toxin on the heart After there are evidences of myocarditis however absolute rest with the least possible voluntary activity must be enforced Adequate fluids must be given to prevent dehydration and shock and 10 per cent dextrose solution may be given intravenously This must be in amounts within the tolerance of the cardiovascular system If however there is vasomotor paralysis and splanchnic dilatation large doses of dextrose solution or of plasma must be given to overcome the shock In this latter situation particularly if the blood pressure is reduced pitressin 0 25 cc to 1 0 cc may be given hypodermically every eight hours until diuresis develops[10] Digitalis is to be avoided as are all but the mildest of sedatives Serum is of no value after the late manifestations of diphtheria have developed

Treatment of Complications The complications of diphtheria usually are due to secondary invading organisms the *Streptococcus hemolyticus* the staphylococcus the pneumococcus the *Hemophilus influenzae* and so forth The diseases caused by these organisms are treated by the appropriate chemotherapeutic agents usually without modification

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dose administered intravenously If the patient rests quietly with this regimen he is watched closely and only supportive treatment is used If however there is evidence of respiratory obstruction tracheotomy is considered This is delayed in most patients as long as the patient is not restless or cyanotic the pulse is strong the respirations are *full and there is no evidence of excessive fatigue* If the pulse (when checked every half hour) begins to mount or fall in rate however when respirations become shallow or irregular or when the aeration of the chest becomes reduced operation is mandatory and must be performed at once Intubation has been abandoned in this hospital chiefly because of the danger that the child will cough up the tube when a skilled operator is not available to replace it and secondly because of the rare patient whose obstruction persists so long that laryngeal stricture results from the irritation caused by the intubation tube in the diseased larynx

Penicillin or sulfadiazine or both are used as an adjunct treatment to control the secondary invaders in all patients with respiratory obstruction These are employed in the customary dose given for systemic infections

Treatment of Cutaneous Diphtheria Antitoxin should be given as soon as the diagnosis can be made by either clinical or bacteriologic means The dose of antitoxin should vary from 20 000 to 100 000 units depending upon the extensiveness duration and severity of the illness The considerations outlined above should govern the mode of administration of serum and other general treatment

Local treatment is also of value Elevation of the extremity to produce better circulation is definitely indicated as is the application of compresses of warm isotonic salt solution containing from 250 to 500 units of penicillin per cubic centimeter This usually will clear the lesion and produce healing within a short time If this is ineffective forcible removal of the membrane once or twice a day with continuation of the compresses has been advised

Treatment of Late Manifestations The neuritis of diphtheria causes danger to life only when the muscles of deglutition and respiration are involved In these instances death formerly resulted but *is no longer inevitable unless there is a coincident severe myocarditis* If there is paralysis of the muscles of deglutition the patient should be placed in the Trendelenburg position and aspiration should be instituted as needed to maintain a free airway and to prevent an aspiration pneumonia This may be employed every few minutes if there is excessive salivation though this usually is not essential If there is excessive salivation or vomiting the patient s nutrition should be maintained through parenteral feedings However if these symptoms are not present feedings can be by gavage *It is our usual practice to* insert a nasal tube each morning give food and fluids at intervals

25 Gas Gangrene

Among the bacilli which grow in wounds under anaerobic conditions there are several which secrete powerful exotoxins The destruction of muscle tissue by these exotoxins the proliferation of the anaerobes and the general toxemia which result make up a classical clinical syndrome called gas gangrene

Most important and most frequently encountered among the organisms which cause gas gangrene are *Clostridium welchii* *Clostridium oedematiens* and *Clostridium septicum* MacLennan[4] found them present in 56 per cent 37 per cent and 19 per cent respectively of 146 cases of this disease acquired from war wounds in the Middle East during World War II Any one of these anaerobes may produce the disease by itself although usually they are associated with each other or with other aerobic and anaerobic bacteria in the wound *Clostridium fallax* *Clostridium bifermentans* *Clostridium histolyticum* and *Clostridium sporogenes* are found less frequently They take part in the mixed infections but seldom produce the disease alone

It is important to note that the presence of these organisms in an infected wound does not always result in the development of gas gangrene Some of the factors contributing to the necrosis and anaerobiosis necessary to produce the disease are (1) deep puncture wounds or lacerations which extend down into the muscle (2) the presence of foreign bodies such as clothing or dirt (3) devitalization of tissue (4) infection with other bacteria and (5) insufficient or late surgical treatment of the wound

North[6] states that among his patients certainly 72 per cent and probably 100 per cent had damage to a major blood vessel He emphasizes the importance of arterial damage as a factor in producing the disease Since these factors are all common to battle wounds gas gangrene is one of the camp followers of wars It frequently accompanies compound fractures Occasionally it develops in an infected uterus after delivery or abortion It may occur after amputation of a limb in a patient with arteriosclerosis or diabetes

Macfarlane[3] states that the toxin destroys the structural framework of the muscles It is probable that both the bacterial toxin and the degeneration products of the affected muscles circulate in the blood and together contribute to the patient s toxicity In addition the intramuscular injection of the toxins of *Cl welchii* and *Cl oedematiens* in dogs was followed by damage to capillaries with subsequent loss of plasma into the muscle and subcutaneous tissue[7 8] This resulted in a

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intra uterine infection material for smear and culture should be obtained from the cervix

The leukocyte count is usually elevated with a proportionate increase in the granulocytes Anemia develops rapidly during gas gangrene and is often profound

In many instances gas is obvious in a roentgenogram of the wound before crepitus can be felt

Diagnosis

Certain clinical criteria are necessary for a diagnosis of gas gangrene pain swelling and tenderness in the vicinity of a wound accompanied by crepitation on pressure and the exudation of the characteristic watery fluid containing gas bubbles and by general toxemia The clinical diagnosis should be confirmed by the demonstration of the organisms in smear and in cultures In the case of intra uterine infection toxemia and foul serosanguineous discharge may arouse the suspicion of gas gangrene although cervical smear and culture will be necessary for the diagnosis

Differential Diagnosis In erysipelas and cellulitis the characteristic odor and discharge the sensation of crepitation and the bubbles of gas will be absent In addition erysipelas shows a sharp line of demarcation with no involvement of the deeper structures In traumatic emphysema there is no edema and no toxemia

Bacteremia caused by any one of a number of different organisms entering through a wound must be differentiated by the lack of the characteristic local signs of gas gangrene and by culture of the infecting organisms from the blood

Prognosis

The prognosis varies tremendously depending upon how soon and how efficiently treatment is given In most groups of war casualties the case fatality rate approximates 50 per cent unless treatment is given early or unless other circumstances are extremely favorable When the wound is in an area where the muscles have good collateral circulation such as the lower leg or the arm the prognosis is much better than in areas where the collateral circulation is poor or excision of tissue is more difficult (such as the thigh buttock shoulder or back)

Prevention

Many cases can be prevented even when the wounds are dirty and are not seen until relatively late if antitoxin containing at least 10 000 *Cl welchii* units 10 000 *Cl septicum* units and 1500 *Cl oedematiens* units is given intramuscularly and excision of all devitalized tissue is carried out Local application of sulfonamides in the wounds will prevent the disease in some cases at least under experimental conditions

decrease in plasma volume and a fall in cardiac output If these events also occur in human infections it is easy to see why the typical picture of shock is often present

Symptoms and Signs

In 90 per cent of cases the clinical evidences of gas gangrene appear within a few hours to a week after the infliction of a wound Occasionally the symptoms may be delayed for several weeks The prodromes are often a sense of heaviness in the affected part followed soon after by pain swelling and edema of the affected part and rapidly increasing toxemia

In the early stages edema and tenderness and sometimes a watery discharge are present around the wound Within a few hours the edema increases A thin dirty pink or blood tinged watery fluid trickles from the wound and pressure around its edges yields a sensation of crepitus and bubbles of gas Pervading the surrounding atmosphere is an odor which has been variously described as mousy musty sickeningly sweet or resembling that of dried fish The skin becomes white from the tension of the edema In the severer cases the skin is discolored red and then dark and is covered by numerous blebs The muscle when exposed appears dry and brick red

The temperature may not rise above 102 F in mild cases whereas in more severely ill patients it reaches 103 to 105° F The pulse rate is increased often out of proportion to the temperature elevation *General toxicity is a characteristic feature When it is fully developed* the patient is restless and apprehensive His face is pinched and gray The pulse is rapid and feeble and may be irregular The bloood pressure is low Coma or delirium may supervene before death

In a smaller proportion of cases the bacteria of gas gangrene produce only a localized abscess containing foul pus with no evidence of involvement of the surrounding muscles and little general toxicity

Complications

The usual complications of wounds may be present such as hemorrhage pulmonary infarction and secondary infection with other organisms

Laboratory and X Ray Examinations

A smear of the wound exudate stained by Gram s method will show a variety of bacteria in most cases with a predominance of large gram positive rods Even if bacteria are few a thorough search will almost always yield these characteristic organisms The *Clostridia* can often be demonstrated in broth cultures with the use of anaerobic methods within twelve to twenty four hours In the case of a suspected

real evidence that it is the slightest aid to recovery No controlled studies have been made of the effect of x rays upon patients while the studies of Erb[1] upon experimental gas gangrene infections show conclusively that x ray irradiation had no demonstrable effect upon *Cl welchii* infections whether used alone or in conjunction with serum

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Penicillin may also aid in preventing the development of gas gangrene probably by controlling the growth of other organisms in the wound Penicillin alone cannot be relied upon to prevent the disease however since gas gangrene has developed in spite of the use of moderately large intramuscular doses prophylactically

TREATMENT

Antitoxin has repeatedly been shown to be a life saving measure when combined with adequate surgery MacLennan[5] found that among sixty six patients treated with serum with or without sulfonamides in addition the fatality rate was 32 per cent as compared with 79 per cent among forty seven patients who received either sulfonamides alone or no specific therapy The vials obtainable commercially each contain a therapeutic dose which is that amount of serum which contains 10 000 units each of *Cl welchii* and *Cl septicum* antitoxin and 1500 units of *Cl oedematiens* antitoxin Small amounts of *Cl sordellii* and *Cl histolyticum* antitoxin are often included in addition Ten or more therapeutic doses should be given intravenously following the procedures for the administration of serum outlined on page 33 These doses should be repeated every twelve to twenty four hours if improvement is not satisfactory

Penicillin Since the *Clostridia* are quite sensitive to penicillin this antibiotic has been widely used While it is probably the wisest course to administer penicillin in all cases it should never be used as a substitute for antitoxin and adequate surgical cleansing After surgical intervention penicillin should be sprinkled in the wound Langley[2] using doses of 20 000 units every two hours intramuscularly along with the two other measures mentioned had a case fatality rate of 11 5 per cent in ninety six cases On the basis of experimental studies Altemeier[9] recommends 8 million or more units a day

Sulfonamides These were formerly given orally to all patients and also placed in the wounds Since the advent of penicillin we see no reason why they need be given systemically They may be used locally in combination with penicillin if desired

Surgery Nothing can take the place of early and thorough surgical treatment All devitalized tissue should be removed all pockets opened and all dirt and debris removed Sometimes this may call for extensive stripping off of muscles and sometimes it may require amputation of a limb Penicillin alone or with a sulfonamide may be sprinkled in the wound after the required operation has been completed Irregular or deep wounds should be left open The affected limb should be immobilized and kept warm Tight dressings or casts shou'd not be used

Transfusions should be given to correct the anemia if the hemoglobin is below 70 per cent or 10 5 gm

X ray therapy has been frequently advocated although there is no

day for adults and proportional doses for children The total daily dose is divided into four equal portions and is administered after each meal and at bedtime Good results are obtained only when the urine is kept at a pH of 5 5 or less Accordingly the administration of alkalis should be avoided and the pH of the urine should be tested with nitrazine paper from time to time The fluid intake should be restricted to 1200 cc per day

Since mandelic acid sometimes produces renal irritation it is unwise to administer it for periods exceeding fourteen days Its use is inadvisable in patients who have a blood urea nitrogen of more than 50 mg per 100 cc and care should be exercised in the treatment of persons in the older age groups

TABLE 51

BACTERIA CAUSING INFECTIONS OF THE URINARY TRACT AND RECOMMENDED TREATMENT

Causative Organism	Drug Recommended	
	First Choice	Second Choice
Escherichia coli *Aerobacter aerogenes* *Alcaligenes faecalis* *Pseudomonas aeruginosa* Paracolon bacilli Other gram negative rods	Sulfonamides or Mandelic acid	Streptomycin
Proteus vulgaris	Sulfonamides	Streptomycin
Streptococcus faecalis	Penicillin	Mandelic acid
Other nonhemolytic (alpha and gamma) streptococci *Streptococcus haemolyticus* Staphylococci	Sulfonamides or Mandelic acid	Penicillin

Sulfonamides Many urinary tract infections caused by the gram negative bacilli will respond to sulfonamides The same is true of many infections due to staphylococci and streptococci with the exception that *Streptococcus faecalis* infections respond poorly In Table 51 we have recommended that the sulfonamides be used first in infections caused by the gram negative rods because of their cheapness and the ease of administration We believe that sulfadiazine is the drug of choice because of its high effectiveness and low toxicity but there is little to choose between it and the other drugs recommended sulfamerazine sulfacetimide and sulfathiazole Sulfonamides should be given in a dose of 3 gm (45 grains) initially followed by 1 gm (15 grains) every six hours Proportional doses may be given to children With these doses renal complications are rare and are avoidable if the urine is alkalinized and sufficient amounts of fluid are given

26 Miscellaneous Bacterial Diseases

Infections with Organisms of the Coli-Aerogenes Group and Related Bacteria

Certain bacteria present in the intestines as parasites under special conditions are potential pathogens These include especially several gram negative nonspore bearing rods *Escherichia coli Aerobacter aerogenes* the paracolon bacilli *Proteus vulgaris* or *morgani* and *Alcaligenes faecalis*

These organisms may be responsible for primary bacteremia peritonitis pyelitis pyelonephritis cystitis and less frequently meningitis[2] and pneumonia

They may be present usually with other organisms in ulcers of the skin or mucous membranes Felty[5] found that the portal of entry in *E coli* bacteremia was the urinary tract in sixteen cases the female genital tract in six the intestinal tract in two a wound infection in one and undetermined in three cases Urinary tract infections are often preceded by obstruction at some point in the urinary tract such as that due to congenital lesions previous infections along the tract prostatic hypertrophy or pressure from external masses The particular organism or combination of organisms causing the infection in the individual case can be determined only by culture of the urine In a study of the effects of treatment with streptomycin[3] the gram negative bacilli were found in the following frequency in infections of the urinary tract

Escherichia coli	151 patients
Pseudomonas aeruginosa	36 patients
Proteus vulgaris	28 patients
Aerobacter aerogenes	22 patients
Alcaligenes faecalis	5 patients

Treatment of Urinary Infections

Before the advent of the newer chemotherapeutic agents many of these infections responded to treatment with alkalis or methenamine or to the administration of large amounts of fluids alone

Mandelic Acid This is a substance which when administered by mouth is not metabolized and is excreted unchanged in the urine It has a bactericidal or bacteriostatic effect against the gram negative rods considered in this section and also against *Shigellae Salmonellae* and *Streptococcus faecalis* It is usually given as calcium or ammonium mandelate (Table 51) in doses of 10 to 16 gm (150 to 240 grains) a

develop a high degree of resistance to streptomycin in a short time Finland[6] demonstrated increases in resistance of more than four thousand fold in patients under treatment for urinary tract infections These occurred in some cases within twenty four hours after the start of streptomycin treatment Resistance is especially likely to develop if obstruction is present in the urinary tract if the infection is caused by more than one organism or if the urine is not kept alkaline

Penicillin Penicillin is particularly helpful in the treatment of urinary tract infections caused by streptococci or staphylococci In most cases the sulfonamides or mandelic acid may be used first because they are less expensive and easier to administer but in severe infections caused by staphylococci and hemolytic streptococci and in all *Streptococcus faecalis* infections penicillin should be used from the start The dose varies depending upon the seriousness of the infection The smallest doses recommended are 25 000 units every three hours or 300 000 units in oil and beeswax every twenty four hours Much higher doses are needed in severe infections

Penicillin is of less value in urinary tract infections caused by the gram negative bacilli although large doses may be effective against many strains as shown by Helmholtz[7]

Summary of Treatment of Urinary Tract Infections 1 A culture should be taken before the start of treatment

2 The presence of obstruction or other pathology in the urinary tract should be searched for If it is found plans should be made to take care of it while the patient is under treatment

3 As shown in Table 51 either sulfonamides or mandelic acid may be used if the infecting organisms are gram negative bacilli with the exception of *Proteus* When *Proteus* is present sulfonamides are the drugs of choice If they are not successful streptomycin should be given

4 If staphylococci or streptococci with the exception of *Streptococcus faecalis* are the etiologic organisms mandelic acid or sulfonamides should be tried first followed by penicillin if they are unsuccessful

5 If *Streptococcus faecalis* is present penicillin is the drug of choice although mandelic acid may be tried first if desired

Treatment of Meningitis

Streptomycin therapy should be started as soon as the diagnosis is made Doses should be 0 05 gm once a day intrathecally and 2 0 to 3 0 gm intramuscularly for each twenty four hour period divided into six four hourly or eight three hourly injections In patients under two years of age these doses may be halved

Since most of these organisms are sensitive to sulfonamides also and since the infections are usually severe it is best to give sulfadiazine in addition Oral doses for adults are 6 gm (90 grains) initially followed by 1 gm (15 grains) every four hours and for children 0 1

Streptomycin Most of the gram negative rods are inhibited by concentrations of streptomycin which are readily obtainable therapeutically Doses recommended for urinary tract infections are from 1 to 3 gm per day divided into six intramuscular doses at four hour intervals The urine should be kept alkaline since streptomycin works best in an alkaline medium We have recommended in Table 51 that streptomycin be used after a preliminary trial with sulfonamides and mandelic acid because the antibiotic is more expensive than sulfonamides and must be administered by injection Furthermore since bacteria often develop resistance to streptomycin rapidly it is best not to employ it until the infection has been carefully studied Obstructive or other pathological conditions present in the urinary tract should be removed before streptomycin therapy is started or preparations should be made to correct them while the patient is being treated with streptomycin Obstruction in the urinary tract and pathological changes such as tumor stone polycystic kidney or chronic nephritis are the most common causes for the failure of streptomycin therapy Other obstacles to success are

TABLE 52

DOSES OF DRUGS USED IN URINARY TRACT INFECTIONS

Drug	*Dose*
Mandelic acid Given as calcium or ammonium mandelate	2 5 to 4 gm (37½ to 60 grains) four times a day and proportional doses for children Keep urine acid and restrict fluid to 1200 cc. per day
Sulfonamides Given as sulfadiazine sulfamerazine sulfacetimide or sulfathiazole	3 gm (45 grains) immediately followed by 1 gm (15 grains) every six hours day and night and proportional doses for children Give 6 gm sodium bicarbonate with the initial dose and 3 gm with each subsequent dose Give 3000 cc of fluids per day and proportional amounts to children
Streptomycin	0 25 to 0 75 gm intramuscularly every four hours day and night Keep urine alkaline
Penicillin	15 000 to 50 000 units intramuscularly every three hours or 300 000 units in oil and beeswax intramuscularly once or twice per day

1 The presence of resistant organisms Resistant strains of any of the gram negative bacteria may be encountered This is particularly true of *Ps aeruginosa* and poor results are often obtained in infections caused by this organism

2 Mixed infections These ordinarily do not respond so well as infections by a single organism

3 Failure to alkalinize the urine

4 The development of resistance during treatment As has been stated in the chapter on Streptomycin (see p 93) bacteria tend to

gm (½ grain) per pound of body weight and 0.06 gm (1 grain) per pound for each twenty four hour period

There is no unanimity of opinion as to whether local or general therapy is preferable or whether the two should be used together Intraperitoneal implantation of sulfonamides has been followed by serious reactions among which hepatitis has been especially frequent Experimental and clinical evidence is accumulating which demonstrates that the systemic route is as good as or better than local implantation and that no advantage is to be gained from the use of both routes Sulfadiazine given systemically appears to be the method of choice

Penicillin Because streptococci and staphylococci are often present penicillin has been employed and has been very successful when large doses are used Crile[4] administered penicillin to fifty patients with peritonitis of appendiceal origin All the patients recovered Half of them developed intra abdominal masses at some time during the course of the disease all of which resolved completely during treatment The dosage which he finally established as being satisfactory was 100 000 units every two hours for six days or longer if clinical signs of peritonitis had not subsided by that time followed by 100 000 units every four hours

Streptomycin Hirshfeld[5] has treated five patients with peritonitis following appendicitis with streptomycin in doses of 1 to 6 gm a day Three patients received penicillin also These three and one other patient recovered The remaining patient was found at autopsy to have pyelophlebitis and liver abscesses Hirshfeld also administered streptomycin to six patients with peritonitis following the perforation of ulcers All six recovered Five received penicillin in conjunction with the streptomycin One patient who had perforation of a carcinoma died after receiving 2 gm of streptomycin a day for thirteen days

Combined Therapy In view of the diversity of bacteria commonly present in peritonitis due to contamination from the gastrointestinal tract the best results will probably be obtained by the use of more than one therapeutic agent Zintel[9] produced peritonitis in dogs by opening the appendix and administering castor oil Only 6.6 per cent of the untreated animals recovered while the following survival rates were obtained with the various therapeutic agents

Systemic streptomycin	[illegible] 4 per cent
Local sulfanilamide systemic sodium sulfadiazine and systemic penicillin	40.0 per cent
Systemic streptomycin plus the above combination	60.0 per cent
Systemic penicillin and systemic streptomycin	70.0 per cent

Although the difference in the results obtained with the last two combinations is not statistically significant it appears that systemic therapy with full doses of penicillin and streptomycin is the most satisfactory method at present available for the treatment of peritonitis due to fecal contamination

gm (1½ grain) per pound of body weight for each twenty four hour period One half of this amount is given initially followed by one-sixth every four hours The same initial doses may be given intra venously in the form of the sodium salt followed by subcutaneous in fusions containing 1 5 gm (22½ grains) every eight hours in adults or one-third of the twenty four hour dose every eight hours for children Complete details of administration can be found in the discussion on Meningococcic Meningitis (p 217)

By the end of forty-eight hours after the start of therapy the streptomycin sensitivity of the organism should have been determined If the organism is resistant to more than 5 micrograms of streptomycin the dose should be increased up to 6 gm a day intramuscularly and 0 1 gm intrathecally The administration of streptomycin and sulfa diazine may be discontinued five to seven days after the temperature has subsided provided that the patient s toxicity has decreased the dextrose concentration of the spinal fluid has returned to normal values and the bacteria have disappeared from this fluid and from the blood Lumbar puncture should be repeated one week later and at weekly intervals thereafter (or sooner if there is any suspicion of a relapse) until the leukocyte count is below 30 per cu mm and all other constit uents are within normal limits The general measures employed are the same as for other types of meningitis (see p 221)

The results obtained in these types of meningitis are not spectacular even with the best of treatment The poor prognosis is probably due to the fact that the infection is already an overwhelming one by the time it reaches the meninges Recoveries from *Escherichia coli* menin gitis have been reported however after treatment with sulfadiazine[9] and streptomycin[1]

Treatment of Peritonitis

Peritonitis following perforation of or operation upon the gastro-intestinal tract is usually a mixed infection containing especially the gram negative rods of the coli aerogenes group and also streptococci and staphylococci The prognosis which was formerly grave has been improved somewhat by the use of the sulfonamides and considerably more by the employment of penicillin or streptomycin

Sulfonamides Various sulfonamides have been used both locally and systemically in the treatment of peritonitis Sulfanilamide sulfa thiazole and sulfadiazine especially have been used locally Amounts up to 10 or 12 gm are dusted into the peritoneal cavity lumping being avoided Sulfathiazole and sulfadiazine have been employed systemi cally The latter is the preferred drug at the present time because of its lower toxicity An initial intravenous dose of 6 gm (90 grains) of sodium sulfadiazine is given initially followed by 1 5 gm (22½ grains) every eight hours by subcutaneous infusion or 1 gm (15 grains) of sulfadiazine every four hours by mouth Children should receive 0 03

gm ($\frac{1}{2}$ grain) per pound of body weight and 0.06 gm (1 grain) per pound for each twenty four hour period

There is no unanimity of opinion as to whether local or general therapy is preferable or whether the two should be used together. Intraperitoneal implantation of sulfonamides has been followed by serious reactions among which hepatitis has been especially frequent. Experimental and clinical evidence is accumulating which demonstrates that the systemic route is as good as or better than local implantation and that no advantage is to be gained from the use of both routes. Sulfadiazine given systemically appears to be the method of choice.

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Systemic streptomycin	2 4 per cent
Local sulfanilamid systemic sodium sulfadiazine and systemic penicillin	10.0 per cent
Systemic streptomycin plus the above combination	60.0 per cent
Systemic penicillin and systemic streptomycin	0 0 per cent

Although the difference in the results obtained with the last two combinations is not statistically significant it appears that systemic therapy with full doses of penicillin and streptomycin is the most satisfactory method at present available for the treatment of peritonitis due to fecal contamination

gm ($1\frac{1}{2}$ grain) per pound of body weight for each twenty four hour period One half of this amount is given initially followed by one sixth every four hours The same initial doses may be given intravenously in the form of the sodium salt followed by subcutaneous infusions containing 1 5 gm ($22\frac{1}{2}$ grains) every eight hours in adults or one third of the twenty four hour dose every eight hours for children Complete details of administration can be found in the discussion on Meningococcic Meningitis (p 217)

By the end of forty eight hours after the start of therapy the streptomycin sensitivity of the organism should have been determined If the organism is resistant to more than 5 micrograms of streptomycin the dose should be increased up to 6 gm a day intramuscularly and 0 1 gm intrathecally The administration of streptomycin and sulfadiazine may be discontinued five to seven days after the temperature has subsided provided that the patient s toxicity has decreased the dextrose concentration of the spinal fluid has returned to normal values and the bacteria have disappeared from this fluid and from the blood Lumbar puncture should be repeated one week later and at weekly intervals thereafter (or sooner if there is any suspicion of a relapse) until the leukocyte count is below 30 per cu mm and all other constituents are within normal limits The general measures employed are the same as for other types of meningitis (see p 221)

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Although the difference in the results obtained with the last two combinations is not statistically significant it appears that systemic therapy with full doses of penicillin and streptomycin is the most satisfactory method at present available for the treatment of peritonitis due to fecal contamination

TREATMENT OF OTHER INFECTIONS

Successful results were obtained with the use of streptomycin in forty-one cases of bacteremia due to gram negative bacilli of the types considered in this chapter [3] while seventeen patients showed no improvement under this therapy Abscesses otitis media, empyema osteomyelitis wound infections and puerperal sepsis have been treated successfully with streptomycin The general principles of antibiotic therapy must be followed here the establishment of drainage when this is needed and the use of methods which will insure adequate concentrations of streptomycin at the place where the bacteria are lodged This may require local administration in some instances systemic administration in others and a combination of the two routes in certain other cases If other bacteria are present in addition to those of the coli aerogenes group penicillin or sulfonamides should be used in conjunction with streptomycin

Pseudomonas Aeruginosa (Pyocyaneus) Infections

Pseudomonas aeruginosa (Bacillus pyocyaneus) is a slender gram negative rod most commonly found as a secondary invader in superficial wounds and elsewhere It is well known to clinicians because of the bluish green pus it produces Upon occasion this organism may enter the blood stream through the skin the genitourinary or gastrointestinal tracts or from the middle ear Bacteremia may be complicated by endocarditis or meningitis Before the advent of the sulfonamides such infections were uniformly fatal

TREATMENT

Sulfonamides and streptomycin are beneficial in pseudomonas infections the latter being the drug of choice for the severer infections The treatment of urinary tract infections caused by these organisms has been discussed along with the infections caused by the coli aerogenes group (p 426) *In cases of sepsis large doses of streptomycin* are needed usually from 3 to 6 gm a day In pyocyaneus meningitis we have used successfully 0 25 gm intrathecally every twelve to twenty four hours along with intramuscular injections of 0 5 gm every three hours

The entire subject of *Ps aeruginosa* infections has been excellently reviewed by Stanley [10] to whose monograph the reader is referred for further information

Streptobacillus Moniliformis Infections (Rat Bite Fever, Haverhill Fever, Erythema Arthriticum Epidemicum)

Streptobacillus moniliformis is a pleomorphic gram negative organism which appears as an interwoven mass of slender filaments and chains of coccoid and bacillary bodies Some of the filaments show

spherical oval fusiform or club-shaped swelling The independent discovery of the organism by a number of different investigators has resulted in a variety of other names assigned to it such as *Streptothrix muris ratti Actinomyces muris* and *Haverhillia multiformis* The organism is a common inhabitant of the nasopharynx of rats the bites of which are the most frequent method of transmitting the organism to man Weasel bites have also been incriminated One epidemic has been reported in which the infection was traced to unpasteurized milk or ice cream[13] in Haverhill Massachusetts

For many years the disease caused by this organism was confused with the rat bite fever caused by *Spirillum minus* (called Sodoku in Japan) Although it has now been definitely established that these are two distinct diseases caused by different etiologic agents it is difficult and sometimes impossible to differentiate them upon clinical grounds alone[12] This will be considered in more detail under Differential Diagnosis

The disease occurs at all ages although it is especially likely to occur in young children and infants Richter[14] has shown that most persons are bitten by rats while they are asleep This accounts for the fact that infants and young children are attacked more often than persons in other age groups and that the commonest sites are the fingers and hands next the feet followed by the face and head and finally the forearm and shoulder

Symptoms and Signs of Rat Bite Fever Due to *Streptobacillus Moniliformis*

The figures given in the following paragraphs refer to twenty six bacteriologically proved cases collected from the literature The incubation period was less than forty eight hours in six cases between three and ten days in ten cases over ten days in nine cases and unknown in one case Although the red streaks of lymphangitis sometimes appeared one to several days after the bite the local lesion usually healed without complications Generalized infection was evidenced by chills chilly sensations malaise and rash or in young children only by fever and irritability An eruption was observed in 85 per cent of the cases most often composed of small maculopapules which faded on pressure and either confined to the face and the extremities or more prevalent in those areas It often involved the palms of the hands and the soles of the feet Petechial and purpuric lesions were sometimes seen especially on the extremities The fever was irregular remittent intermittent or relapsing and varied from a slight amount to temperatures of 104° and 105 F

Arthritis was present in 16 per cent of the cases Usually more than one joint was involved In the patients observed before penicillin was available the arthritis often lasted for months or years

Regional lymphadenopathy was fairly frequent General lymphadenopathy or enlargement of the spleen was less common Edema of the vocal cords and of the extremities and subcutaneous abscesses were occasionally seen

Symptoms and Signs of the Epidemic Type (Erythema Arthriticum Epidemicum)

These are based upon the report of Place [13] who studied an epidemic which involved eighty six persons After an incubation period of one to three days the onset was abrupt usually with a chill vomiting or a severe headache Chills were present at some time in the disease in 95 per cent of the patients vomiting in 61 per cent and headache in 56 per cent Fever varied from a slight amount up to a temperature of 105° F It was characteristically present in two distinct courses separated by an afebrile period of two to three days Rash was observed in 93 per cent of the patients and may have been present and unrecognized in the remainder In general it was similar in distribution and appearance to the rash of rat bite fever Arthritis sore throat cough and dysphagia were also encountered

Laboratory Examinations

The blood culture is the most important diagnostic test It should be positive in every case when proper procedures are employed These methods as well as the characteristics of the organism have been completely described by Brown [12] The same author has also devised an agglutination test by means of which he obtained titers of 1 1280 to 1 5120

The leukocyte count is usually between 10 000 and 15 000 per cu mm although it may be within normal limits or may rise as high as 30 000 per cu mm

Diagnosis

The history of a bite by a rat or other rodent the number and frequency of the general symptoms compared with the benign appearance of the local lesion the characteristic morbilliform or rubelliform rash and the polyarthritis when present should point to the likelihood of rat bite fever due to *Streptobacillus moniliformis* Absolute diagnosis can be made only by cultivating the organisms from the blood This is especially true in the epidemic type Antigens for the agglutination tests are not usually available in most laboratories

Differential Diagnosis While many authors have attempted to differentiate the streptobacillary and spirillar types of rat bite fever upon clinical grounds we agree with Brown [12] that it is impossible to make the distinction in a particular patient without recourse to laboratory procedures It is probable that the streptobacillary form is

the one more frequently encountered in the United States while the spirillar is more prevalent in the Orient The *Spirilla* can be obtained by inoculation of the patient s blood into guinea pigs or white mice

Individual features of rat bite fever may cau e confusion with other diseases The rash must be differentiated from that seen in measles German measles typhoid and salmonella fevers typhus and Rocky Mountain spotted fevers meningococcic infections and the bacteremias

The arthritis may resemble that which occurs in gonococcic or meningococcic infections brucellosis shigella dysentery acute rheumatic fever and acute rheumatoid arthritis

Prognosis

As far as life is concerned the prognosis is good Even before the advent of penicillin nearly all the patients recovered On the other hand the morbidity was a serious feature since it involved weeks of fever and sometimes months or years of arthritis

Prevention

There is no method of prevention except the elimination of rats a public health measure which should be pursued diligently and relentlessly in every community in order to prevent this and other diseases

Treatment

None of the measures used before penicillin proved to be of any value These included arsphenamine and the sulfonamides Penicillin has a specific effect upon the organism and usually produces improvement in the disease Altemeier[11] found that the *Streptobacillus* in one case was sensitive to less than 0 05 unit of penicillin per cc and in two other cases to between 0 05 and 0 10 unit per cc Sprecher[14] encountered a relatively resistant strain which was sensitive to 0 80 unit of penicillin per cc but which was extremely sensitive to streptomycin

At least twelve patients with the streptobacillary form of rat bite fever have been treated with penicillin including three by Altemeier[11] and four by Wheeler [15] Although rather small doses have been employed successfully in some cases it is best to give at least 20 000 units intramuscularly at three hour intervals and to continue this dose until the temperature has been normal for two days With these doses the temperature should begin to fall within twelve to twenty four hours and in most instances should be within normal limits in forty eight to seventy two hours The toxicity and rash usually disappear early while the arthritis subsides more gradually Relapse occurred in two patients who received smaller doses than those recommended

In each instance it responded to further penicillin therapy Subcutaneous abscesses may require surgical drainage

One case of epidemic *Streptobacillus moniliformis* infection has been reported[14] in which the response to 30 000 units of penicillin every three hours was unsatisfactory When the organism was found to be susceptible to streptomycin and 0 3 gm of this antibiotic was administered at three-hour intervals the fever dropped and the symptoms subsided Although it is likely that larger doses of penicillin would have produced a favorable response this case illustrates that some patients with *Streptobacillus moniliformis* infections can be treated most satisfactorily with streptomycin

Glanders

Glanders is a disease of horses donkeys and mules which is caused by small slender gram negative rods called *Pfeifferella mallei* and is occasionally communicated to man It is found among persons who work around the animals mentioned and develops from contact with infected nasal discharge or with pus from the ulcers and pustules Rarely it is transmitted by inhalation

Symptoms and Signs

The clinical course in man may be acute or chronic The former is characterized by fever with or without chills severe prostration a mucopurulent nasal discharge and sometimes a generalized pustular eruption Weakness headache anorexia and joint pains are other manifestations It terminates fatally within one to three weeks

In the chronic form nodules develop in the skin muscles and bones with hard swelling of the regional lymphatics The cutaneous nodules may ulcerate

Howe[18] has reported six cases of glanders acquired in the laboratory apparently by the respiratory route The incubation period varied from ten to fourteen days The onset was insidious in five of the six patients Headache general aching low grade fever and fatigue were the common symptoms Chest pain photophobia chills and nuchal rigidity were sometimes present Circumscribed or irregular areas of density were present in the chest roentgenograms of five patients Only one patient exhibited leukocytosis The disease lasted from three weeks to nine months All the patients recovered after receiving sulfadiazine Other details regarding this rare disease will be found in the references cited[16, 17, 19]

Laboratory Examinations

Stained smears made from the pus or discharge from the lesions of man or animals usually show the organisms intracellularly and extracellularly They can be obtained by culture or by inoculation into

guinea pigs The organism can also be cultured from the blood Agglutination and complement fixation tests are positive in most instances Howe[15] considered an agglutinin titer of 1 320 or higher or a complement fixation titer of 1 20 or higher to be diagnostic He found that the mallein skin test became positive as antibodies developed For this purpose 0 1 cc of a 1 10 000 dilution of commercial mallein was injected intracutaneously The test was considered positive if an area of erythema of 1 0 cm or more was present forty-eight hours later

DIAGNOSIS

A history of contact with horses or mules together with the local lesions and the signs of an infection should make one suspicious of glanders Bacteriologic diagnosis of the animal and of the human lesions agglutination complement fixation and intracutaneous tests are confirmatory

PROGNOSIS

Few human patients recovered before the advent of sulfonamides

TREATMENT

Sulfadiazine has been found to be an effective therapeutic agent in experimental animals and in human infections[15] It should be given in doses of 6 gm (90 grains) immediately followed by 1 gm (15 grains) every four hours

Botulism

Clostridium botulinum is a spore-bearing gram positive anaerobic rod The fulminating highly fatal disease caused by the powerful exotoxin of this saprophytic organism is called botulism The causative organism multiplies in food which has been imperfectly preserved by smoking pickling or canning and then allowed to stand for some time This permits the toxin to be formed before the food is eaten When the toxin is absorbed from the gastrointestinal tract it apparently acts by paralyzing the nerve endings at the myoneural junctions Tiny doses of 0 01 mg or less may be fatal for man

Cl botulinum organisms have been divided into several types each of which produces its specific toxin Only type A and B toxins have been found in man

SYMPTOMS AND SIGNS

The incubation period in most cases is about eighteen to thirty six hours the extremes being two hours to three or four days In about one-third of the patients gastrointestinal disturbances appear first nausea vomiting diarrhea and abdominal pain Later in these cases and at the onset in the remainder come the evidences of nerve involve

ment Particularly frequent are the eye signs diplopia ptosis and dilatation of the pupils Difficulty in swallowing speaking and breathing and dizziness are also common Other nerve paralyses occur less often Along with pronounced prostration and rapid pulse there is a normal temperature and a clear sensorium Death comes from respiratory failure strangulation or circulatory failure If the patient recovers the nerve palsies clear up slowly

Laboratory Examinations

Injection of the suspected food into mice will produce paralyses and death

Diagnosis

This can usually be made from a history of eating improperly preserved (usually home canned) food especially if other persons have eaten the food and have developed a similar disease The suspected food is likely to have had an abnormal appearance or odor to have contained gas bubbles or to have come from bulged cans Such foods and also even normal appearing foods if they seem to be implicated should be examined *if they can be obtained*

Differential Diagnosis Other diseases which cause similar neurological symptoms must be differentiated from botulism These include poliomyelitis encephalitis meningitis poisoning by mushrooms belladonna methyl alcohol and other substances

Prognosis

One half to two thirds of the patients die unless they receive serum early in the course of the disease

Prevention

The only way to prevent the disease is to can food properly and to refrain from eating any food which does not appear to have been properly preserved or which gives the slightest appearance of being spoiled Such food should not even be tasted since even a spoonful may contain enough toxin to cause death It must be emphasized however that even apparently unspoiled food may on rare occasions contain the toxin

Treatment

Polyvalent serum containing antitoxin against types A and B toxin should be given as early in the course of the disease as possible[20, 21, 22] After the precautions against allergic reactions have been taken (see p 33) 20 000 units should be injected intravenously This should be

repeated every eight to twelve hours until there are definite evidences of recovery

If symptoms begin within a few hours of the ingestion of the food the stomach should be lavaged with a solution of sodium bicarbonate A large enema should be given Secretions should be aspirated from the pharynx and from the larynx when necessary If paralysis of the respiratory muscles occurs it is imperative that the patient be placed in a respirator immediately

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Appendix

Determination of Sulfanilamide* in Blood and Urine[1]

REAGENTS

1 A solution of trichloroacetic acid containing 15 gm dissolved in water and diluted to 100 cc

2 A 0 1 per cent solution of sodium nitrite

3 An aqueous solution of N (1 naphthyl)ethylenediamine dihydrochloride containing 100 mg per 100 cc This solution should be kept in a dark colored bottle

4 A solution of saponin containing 0 5 gm per liter

5 4 N hydrochloric acid

6 A solution of ammonium sulfamate containing 0 5 gm per 100 cc

7 A stock solution of sulfanilamide in water containing 200 mg per liter This solution can be kept for several months in the ice box The most convenient standards to prepare from the stock solution are 1 0 5 and 0 2 mg per cent To prepare these 5 2 5 and 1 cc of the stock solution plus 18 cc of the 15 per cent solution of trichloroacetic acid are diluted to 100 cc

Procedure for Blood † 2 cc of oxalated blood are measured into a flask and diluted with 30 cc of saponin solution and after 1 or 2 minutes precipitated with 8 cc of the solution of trichloroacetic acid The free sulfanilamide is determined in the filtrate as follows 1 cc of the sodium nitrite solution is added to 10 cc of the filtrate After 3 minutes standing 1 cc of the sulfamate solution is added and after 2 minutes standing 1 cc of the solution of N (1 naphthyl)ethylenediamine dihydrochloride is added The unknown is compared with an appropriate standard which has been treated as above This comparison can be made immediately and no change in color is observed for 1 hour or more To determine the total sulfanilamide 10 cc of the filtrate are treated with 0 5 cc of 4 N hydrochloric acid heated in a boiling water bath for 1 hour cooled and the volume adjusted to 10 cc The subsequent procedure is as stated above for determining free sulfanilamide

Procedure for Urine Protein free urine is diluted to contain about 1 to 2 mg per cent of sulfanilamide and 50 cc of the diluted urine plus 5 cc of the 4 N hydrochloric acid are diluted to 100 cc 10 cc of the product of this second dilution are treated as a blood filtrate for free

* The same procedure is used for other sulfonamides In such cases the standard is made up with the drug to be determined

† Sample and reagent volumes can be proportionately reduced to give the minimal amount of filtrate necessary for an accurate color comparison

sulfanilamide and 10 cc heated without further addition of acid for total sulfanilamide If the urine contains protein it is diluted and treated by the procedure for blood *

A photoelectric colorimeter may be used The reader is referred to the article by Bratton and Marshall[1] for the technique

Penicillin Assay (Modified Rammelkamp Method)

1 *If the specimen to be assayed is known to be contaminated it* should first be sterilized in a Seitz or similar filter

2 Using sterile technique place 0 2 cc of tryptose phosphate broth in all but the first of a series of twelve small tubes

3 Add 0 2 cc of the serum or fluid being tested in the first tube 0 2 cc in the second tube and mix Remove 0 2 cc and place in the third tube mix and remove 0 2 cc and continue this procedure to the twelfth tube discarding the last 0 2 cc

4 Make a duplicate series using a standard solution of 5 units per cc of penicillin instead of the unknown serum or fluid

5 To all tubes add 0 5 cc of a 10^{-4} dilution of a twenty four hour culture of *Streptococcus hemolyticus* C203 in tryptose phosphate broth containing 1 per cent Type O blood

6 Calculations

Unknown	Tube	1	2	3	4	5	6	7	8 etc
	Dilution	1	1 2	1 4	1 8	1 16	1 32	1 64	1 128
	Growth (example)	0	0	0	0	+	+	+	+

Standard	Tube	1	2	3	4	5	6	7	8 etc
	Units of penicillin per 0 2 cc	1	0 5	0 25	0 125	0 0625	0 0312	0 0156	0 0078
	Growth	0	0	0	0	0	0	0	+

Since 0 0156 unit of penicillin per 0 2 cc or 0 078 unit per cc inhibits the streptococcus strain in the standard series then tube 4 of the unknown in which the streptococcus is also inhibited contains an equivalent amount of penicillin i e 0 078 unit per cc

0 078 × 8 (dilution correction) = 0 625 unit per cc in the unknown

Streptomycin Assay[3]

B circulans is a mesophilic motile aerobic spore bearing micro organism It grows well at temperatures between 30 and 37°C forming floccules which make the end point in the serial dilution test relatively easy to determine It is sensitive to 0 15 microgram/ml of streptomycin base Broth cultures are quite stable and may be preserved in screw cap bottles under refrigeration for periods of one month with no appreciable loss in sensitivity

* Quoted from Bratton A C and Marshall E K Jr New Coupling Component for Sulfanilamide Determination J Biol Chem *128* [illegible] 1939 by permission of the authors and the publisher

"**Technique of the Test** Amounts (0 5 ml) of the modified nutrient broth are placed in sterile Wassermann tubes and serial dilutions by halves made by adding 0 5 ml of the fluid being tested to one of the tubes and carrying 0 5 ml by serial dilution for the desired number of tubes The first tube in the series contains 0 5 ml of the solution under test only A standard is prepared for comparison by diluting a streptomycin salt of known potency in broth to contain 10 micrograms of the base per milliliter This standard is serially diluted in the same manner as the body fluid under test One and one half milliliter of a 1 100 dilution of the test organism in broth is then added to all tubes after which they are incubated overnight The last tube in which no growth occurs is considered the end point

The concentration of streptomycin in the unknown is then determined by comparing the end point with that of the standard An example is given in the table in which it will be noted that the standard completely inhibited growth of *B circulans* in the fifth tube Since this represents 10 micrograms the serum tested contains one fourth as much or 2 5 micrograms the urine which caused complete inhibition in the fourth tube contained 5 micrograms × 50 or 250 micrograms ml To determine lower potencies it is necessary to vary the dilution series of standard and unknown *

TABLE 1

Fluid	Tube No s						
	1	2	3	4	5	6	7
Standard	0	0	0	0	0	+	+
Serum	0	0	0	+	+	+	+
Urine 1 50	0	0	0	0	+	+	+

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Quoted from Price C S Nielson J K and Welch H The Estimation of Streptomycin in Body Fluids Science *103* 56 1946 by permission of the publisher

INDEX

NOTE In this index the expression *vs* has been used to denote differential diagnosis Thus Abscess subphrenic *vs* pleurisy with effusion is the equivalent of Abscess subphrenic differential diagnosis with pleurisy with effusion